Monitoring of Nonsteroidal Immunosuppressive Drugs in Patients With Lung Disease and Lung Transplant Recipients

American College of Chest Physicians Evidence-Based Clinical Practice Guidelines

Robert P. Baughman, MD, FCCP; Keith C. Meyer, MD, FCCP; Ian Nathanson, MD, FCCP; Luis Angel, MD, FCCP; Sangeeta M. Bhorade, MD, FCCP; Kevin M. Chan, MD, FCCP; Daniel Culver, DO, FCCP; Christopher G. Harrod, MS; Mary S. Hayney, PharmD, MPH; Kristen B. Highland, MD; Andrew H. Limper, MD, FCCP; Herbert Patrick, MD, FCCP; Charlie Strange, MD, FCCP; and Timothy Whelan, MD, FCCP

Objectives: Immunosuppressive pharmacologic agents prescribed to patients with diffuse interstitial and inflammatory lung disease and lung transplant recipients are associated with potential risks for adverse reactions. Strategies for minimizing such risks include administering these drugs according to established, safe protocols; monitoring to detect manifestations of toxicity; and patient education. Hence, an evidence-based guideline for physicians can improve safety and optimize the likelihood of a successful outcome. To maximize the likelihood that these agents will be used safely, the American College of Chest Physicians established a committee to examine the clinical evidence for the administration and monitoring of immunosuppressive drugs (with the exception of corticosteroids) to identify associated toxicities associated with each drug and appropriate protocols for monitoring these agents.

Methods: Committee members developed and refined a series of questions about toxicities of immunosuppressives and current approaches to administration and monitoring. A systematic review was carried out by the American College of Chest Physicians. Committee members were supplied with this information and created this evidence-based guideline.

Conclusions: It is hoped that these guidelines will improve patient safety when immunosuppressive drugs are given to lung transplant recipients and to patients with diffuse interstitial lung disease.

CHEST 2012; 142(5):e1S–e111S

Abbreviations: ACCP = American College of Chest Physicians; ALT = alanine aminotransferase; ATG = antithymocyte globulin; CHF = congestive heart failure; CMV = cytomegalovirus; CNi = calcineurin inhibitor; COI = conflict of interest; CsA = cyclosporin A; FDA = US Food and Drug Administration; HBV = hepatitis B virus; HMG-CoA = β -hydroxy- β -methylglutaryl-coenzyme A; HSP = Health and Science Policy Committee; IL2RA = IL-2 receptor α ; ILD = interstitial lung disease; IPF = idiopathic pulmonary fibrosis; ITP = idiopathic thrombocytopenia purpura; LAM = lymphangioleiomyomatosis; MESNA = sodium 2-sulfonylethanesulfonate; MPA = mycophenolic acid; mTOR = mammalian target of rapamycin; PTLT = posttransplant lymphoproliferative disease; RCT = randomized controlled trial; SIRS = systemic inflammatory response syndrome; TNF = tumor necrosis factor; TPMT = thiopurine methyltransferase

SUMMARY OF RECOMMENDATIONS

3.0 Monitoring of Nonsteroidal Immunosuppressive Drugs in Patients With Lung Disease and Lung Transplant Recipients

3.1 Anti-Tumor Necrosis Factor- α (TNF- α) Agents

For editorial comment see page 1081
For related article see page 1284

3.1a. For patients who will undergo anti-TNF- α therapy, a chest radiograph is recommended prior to treatment (Grade 1C).

3.1b. For patients who will undergo anti-TNF- α therapy, a tuberculin skin test is recommended to screen for latent TB prior to treatment (Grade 1C).

3.1c. For patients who will undergo anti-TNF- α therapy and present with a chest radiograph consistent with prior TB or a positive tuberculin skin test and/or are high-risk individuals, active TB infection should be excluded prior to treatment with adalimumab (Grade 1C), etanercept (Grade 1B), or infliximab (Grade 1B).

3.1d. For patients with latent *Mycobacterium tuberculosis*, active prophylactic treatment following published guidelines before initiation of anti-TNF- α therapy is recommended (Grade 1B).

3.1e. For patients with latent *M tuberculosis* who will undergo anti-TNF- α therapy, close monitoring for TB is recommended for up to 6 months after discontinuing therapy (Grade 1C).

3.1f. For patients who develop symptoms indicative of TB, prompt evaluation for active disease is recommended (Grade 1C).

3.1g. For patients with known grade III or IV New York Heart Association class heart failure, administration of adalimumab (Grade 1C), etanercept (Grade 1C), and infliximab (Grade 1B) is not recommended.

3.1h. For patients with a history of congestive heart failure (CHF) who undergo anti-TNF- α therapy, close observation for CHF exacerbation is recommended (Grade 1C).

3.1i. For patients with a history of demyelinating disease, administration of etanercept is not recommended (Grade 1C), and administration of adalimumab and infliximab is not suggested (Grade 2C).

3.1j. For patients with no history of demyelinating disease who undergo anti-TNF- α therapy and experience symptoms or display signs of a demyelinating process, discontinuation of therapy is suggested (Grade 2C).

3.1k. For patients who undergo anti-TNF- α therapy and develop symptoms of a lupus-like disorder, discontinuation of therapy is suggested (Grade 2C).

3.1l. For patients who will undergo anti-TNF- α therapy and who are at risk for viral hepatitis, serologic screening for hepatitis B is recommended prior to treatment (Grade 1C).

3.1m. For patients who have hepatitis B virus infection, anti-TNF- α therapy should not be administered (Grade 1C).

3.1n. For patients who undergo anti-TNF- α therapy and develop unresolved infections, discontinuation of treatment until the infection is resolved is recommended (Grade 1B).

3.1o. For patients who are pregnant, administration of anti-TNF- α therapy is used only if alternatives are not able to be used (Grade 2C).

3.2 Calcineurin Inhibitors (CNIs)

3.2a. For patients who will undergo CNI therapy, the monitoring of drug concentrations, BP, glucose, potassium, magnesium, lipids, CBC count, and renal function is recommended (Grade 1B).

3.2b. For patients who undergo CNI therapy, monitoring of drug levels when CYP3A4 inducers or inhibitors are added or stopped and adjusting doses are recommended when using cyclosporin A (Grade 1A) or tacrolimus (Grade 1B) therapy.

3.2c. For lung transplant recipients receiving CNI therapy who develop renal dysfunction, a reduction in the target dose concentration is suggested (Grade 2C).

Accepted March 6, 2012.

Affiliations: From the University of Cincinnati (Dr Baughman), Cincinnati, OH; University of Wisconsin School of Medicine and Public Health (Dr Meyer), Madison, WI; University of Central Florida (Dr Nathanson), Orlando, FL; University of Texas Health Sciences (Dr Angel), San Antonio, TX; University of Chicago Hospitals (Dr Bhorade), Chicago, IL; University of Michigan Health Systems (Dr Chan), Ann Arbor, MI; Cleveland Clinic (Dr Culver), Cleveland, OH; American College of Chest Physicians (Mr Harrod), Northbrook, IL; University of Wisconsin School of Pharmacy (Dr Hayney), Madison, WI; Medical University of South Carolina (Drs Highland and Strange), Charleston, SC; Mayo Clinic College of Medicine (Dr Limper), Rochester, MN; Drexel University College of Medicine (Dr Patrick), Philadelphia, PA; and University of Minnesota (Dr Whelan), Minneapolis, MN.

Disclaimer: American College of Chest Physician guidelines are intended for general information only, are not medical advice, and do not replace professional medical care and physician advice, which always should be sought for any medical condition. The complete disclaimer for this guideline can be accessed at <http://www.chestnet.org/accp/guidelines/functions-process>.

Correspondence to: Robert P. Baughman, MD, FCCP, University of Cincinnati, Holmes Bldg, Room 1001, PO Box 670565, Eden Ave and Albert Sabin Way, Cincinnati, OH 45267-0565; e-mail: bob.Baughman@uc.edu

© 2012 American College of Chest Physicians. Reproduction of this article is prohibited without written permission from the American College of Chest Physicians. See online for more details. DOI: 10.1378/chest.12-1044

3.3 Antilymphocyte Antibodies

3.3a. For patients who undergo antilymphocyte antibody therapy, monitoring for infusion reactions is recommended (Grade 1B).

3.3b. For patients who undergo antithymocyte globulin or muromonab therapy, monitoring of CBC counts and liver function tests is recommended during therapy (Grade 1B).

3.3c. For patients with lung disease and lung transplant recipients who will undergo antithymocyte globulin or muromonab therapy, laboratory evaluation for host antibodies (where available) before reinstitution of therapy is suggested (Grade 2C).

3.3d. For patients who undergo muromonab therapy, monitoring for pulmonary edema and systemic inflammatory response syndrome during therapy is recommended (Grade 1B).

3.4 IL-2 Receptor Antagonists

3.4a. For patients who undergo IL-2 receptor antagonist therapy, monitoring for infusion reactions is recommended (Grade 1C).

3.4b. For patients who undergo IL-2 receptor antagonist therapy, monitoring of renal function, CBC counts, and infection is recommended (Grade 1C).

3.4c. For patients who undergo IL-2 receptor antagonist therapy, the simultaneous use of either basiliximab (Grade 1C) or daclizumab (Grade 1B) with antilymphocyte antibodies is not recommended.

3.5 Cytotoxic Agents

3.5a. For patients who will undergo concurrent therapy with azathioprine and allopurinol, a reduction in dose of azathioprine is recommended (Grade 1A).

3.5b. For patients who undergo azathioprine therapy, obtaining CBC counts and renal/hepatic profiles every 1 to 3 months is recommended (Grade 1B).

3.5c. For patients who will undergo cyclophosphamide therapy, monitoring of CBC count, renal profile, and urinalysis at least monthly for dose adjustment is recommended (Grade 1B).

3.5d. For patients who will undergo cyclophosphamide therapy, increased fluid intake (eg, 2 L

in addition to normal intake in adults; additional volume given to children needs to be calculated on the basis of body weight) on the days of therapy is recommended (Grade 1C).

3.5e. For patients who undergo or have undergone cyclophosphamide therapy and develop hematuria, further evaluation is recommended (Grade 1B).

3.5f. For patients who will undergo leflunomide or methotrexate therapy, screening for the use of alcohol and chronic viral hepatitis prior to treatment is recommended (Grade 2C).

3.5g. For patients who undergo methotrexate or leflunomide therapy, performance of liver function tests and CBC counts is recommended (Grade 1C).

3.5h. For patients who undergo methotrexate therapy, folic acid supplementation is recommended (Grade 1A).

3.5i. For patients who undergo leflunomide therapy and develop neuropathic symptoms, prompt consideration of discontinuing therapy and washing out with cholestyramine is recommended (Grade 1C).

3.5j. For patients who undergo methotrexate (Grade 1B) or leflunomide (Grade 1C) therapy and develop new or worsening signs or symptoms of lung disease, further evaluation is recommended.

3.5k. For patients who undergo methotrexate therapy and develop persistently elevated liver transaminases above their own baseline, cessation of treatment or evaluation by liver biopsy is recommended (Grade 1B).

3.5l. For patients with renal insufficiency, ascites, or pleural effusions who undergo methotrexate therapy, decreased methotrexate clearance may be present, and dose reduction may be required (Grade 2C).

3.5m. For patients who undergo mycophenolic acid therapy and develop adverse GI effects, including diarrhea, interruption of therapy or reduction in dose is recommended (Grade 1B).

3.5n. For patients who undergo mycophenolic acid therapy and develop signs or symptoms of progressive multifocal leukoencephalopathy, cessation of treatment is suggested (Grade 2C).

3.6 *Mammalian Target of Rapamycin (mTOR) Inhibitors*

3.6a. For patients who will undergo mTOR inhibitor therapy, obtaining cholesterol and triglyceride levels prior to treatment is recommended (Grade 1B).

3.6b. For patients who present with an abnormal elevation of fasting triglycerides, avoidance of mTOR therapy or careful monitoring of triglycerides is recommended (Grade 1B).

3.6c. For patients who undergo mTOR therapy, monitoring for hyperlipidemia is recommended (Grade 1A).

3.6d. For patients who undergo mTOR therapy, monitoring of CBC counts, creatinine, and BP is recommended (Grade 1B).

3.6e. For patients who undergo sirolimus therapy, monitoring of drug concentration is recommended (Grade 1B).

3.6f. For lung transplant recipients scheduled to undergo sirolimus therapy, administration of sirolimus during the early perioperative period is contraindicated due to the risk of airway dehiscence (Grade 1A).

3.6g. For patients who undergo sirolimus therapy and are at risk for poor wound healing, consideration of dose adjustments or an alternative therapy to lower this risk is suggested (Grade 2C).

3.6h. For patients who undergo sirolimus therapy and develop new or worsening respiratory symptoms or signs, an evaluation for sirolimus-induced pulmonary toxicity is recommended (Grade 1B).

3.7 *Other Immunosuppressive Drugs*

3.7a. For patients receiving hydroxychloroquine and chloroquine, an eye examination at least once per year is suggested (Grade 2B).

3.7b. For patients who undergo imatinib mesylate therapy, monitoring of CBC and hepatic function is suggested (Grade 2C).

Various conditions require the use of nonsteroidal immunosuppressive agents, and drugs that suppress and modulate host immunity are commonly prescribed for patients with diffuse infiltrative lung

disease and for lung transplant recipients. Early recognition of conditions that require immunosuppressive therapy and prompt administration of immunosuppressive agents can prevent or minimize tissue injury and prevent irreversible decline in organ function. Because these medications can be harmful, timely detection and remediation of clinically significant side effects can improve the benefit/risk ratio for patients receiving them. The lack of a guideline that comprehensively reviews available evidence prompted the American College of Chest Physicians (ACCP) to convene a committee of experts to specifically examine experience with pharmacologic agents used to treat individuals with diffuse infiltrative lung disease and lung transplant recipients. The committee used an evidence-based approach to develop a concise, but comprehensive review to guide the administration of nonsteroidal immunosuppressive agents to patients with pulmonary disorders and for monitoring them to detect adverse consequences from these agents.

The objective of this guideline is to provide recommendations for monitoring the use of these drugs so that clinically significant side effects can be either avoided or recognized in a timely fashion. This guideline intentionally does not provide any recommendations concerning indications for use of these drugs. Rather, it should be used exclusively to achieve maximal patient safety when these medications are prescribed. For some drugs, sufficient information related solely to treating pulmonary diseases was available. For other drugs, however, recommendations were partially or entirely abstracted from nonpulmonary studies. As the guideline focuses on common and unique side effects associated with specific drugs, it can provide important information to both physicians and patients. To maximize patient safety, readers are also encouraged to use other resources (eg, package inserts and regulatory agency guidelines, such as the US Food and Drug Administration [FDA] MedWatch program, Micromedex, and Arthritis Foundation statements and guidelines).

1.0 METHODS

In 2005, the ACCP Health and Science Policy Committee (HSP) initiated a project to develop a guideline to provide recommendations on the administration and monitoring of nonsteroidal immunosuppressive drugs used to treat lung diseases and lung transplant recipients. Some of the data have been extrapolated from other areas of immunosuppression, such as the treatment of rheumatological disorders, and from nonsteroidal immunosuppressive regimens used for recipients of solid organ transplants other than lung. For each drug, the reviewers examined any recommendations and guidelines for nonpulmonary indications. The ACCP methodologist, who also provided

oversight for the development of evidence tables, conducted the literature review. Each article was reviewed by the methodologist as well as by two panel reviewers. The studies were graded using ACCP guidelines, which are detailed later in this section. Data were summarized into evidence tables.

1.1 Expert Panel Composition

The guideline panel was organized according to ACCP policy. Membership was obtained through open nomination from the ACCP membership. Panel members were selected based on clinical and methodological expertise and represent a wide range of specialists in this field. The panel met for a 2-day meeting to review the evidence and structure the guideline. All other business was handled through conference calls and electronic means. Writing assignments were determined by panel members' known expertise in the specific drug areas. Each section of the guideline was assigned one primary and one secondary author. In addition, a pediatric expert provided input to sections that were relevant to children's health care. A final meeting was convened with the committee members to review and approve the recommendations.

1.2 Conflict of Interest

From the outset, each member completed a conflict of interest (COI) form to be kept on file with ACCP. In addition, panel members updated COI forms at the face-to-face meeting and verbally related any changes in conflict status during conference calls. Final disclosures were collected at the time of submission for publication, which are those listed herein. Section authors were assigned only

if no conflicts were related to the drug. Those with a conflict were considered for reassignment to another drug for which they had no conflict. Panel members also abstained from voting on final recommendations on any drug for which they had a COI. COI included involvement in a grant-supported study of the drug during the prior 5-year period.

2.0 SCOPE OF THE WORK

This evidence-based guideline focuses on the monitoring of 20 immunomodulatory drug agents used in the treatment of patients with lung disease and lung transplant recipients. The specific research questions the panel addressed are summarized in Table 1. Inclusion criteria are defined in Table 2.

The project scope of work included an evidence review accompanied by the establishment and grading of recommendations. Each task is described in greater detail in the following sections.

2.1 Review of Evidence

The literature review was based on the research questions and inclusion criteria as defined in Tables 1 and 2, respectively. The literature review was conducted through a comprehensive Medline search from 1980 through February 2008 and supplemented by articles supplied by the guideline panel, bibliographies and reference lists from reviewed articles, and other existing systematic reviews. The literature

Table 1—Summary of Clinical Research Questions

Subject/Topic	Clinical Questions
Respiratory disorders and conditions treated with immunosuppressive drugs	Which respiratory disorders and conditions are typically or frequently treated with immunosuppressive/immunomodulatory agents?
Toxic/adverse events	What are the toxic/adverse events associated with the use of these defined agents? Adverse events include the following: Serious infection Opportunistic infection (TB, fungi) Malignancies Neurotoxicity/demyelination Hematologic abnormalities Administration reactions Cardiotoxicity Nephrotoxicity Autoantibodies and lupus Hepatotoxicity Pulmonary toxicity
Administration protocols	What are the typical administration protocols (route, dose, interval) for these agents? What is the evidence for administration protocol in children?
Monitoring for toxic/adverse events	What is the evidence for monitoring patients for toxicity/adverse events (types of testing, frequency of testing)?
Calcineurin inhibitors and acute or chronic lung transplant rejection	With regard to lung transplant patients, what is the evidence for: Lower vs higher levels of calcineurin inhibitors to reduce acute or chronic rejection? Nephrotoxicity of calcineurin inhibitor? Monitoring for these specific patients?

Table 2—Criteria for Inclusion of Studies

Variable	Description
Patients	Patient with diffuse infiltrative/inflammatory lung disease, excluding airway disorders (eg, asthma, COPD, bronchiectasis) and lung transplant recipients
Control group	Patients treated for malignancy; patients treated for rheumatologic disorder; nonpulmonary organ transplant recipients
Exposure/intervention	Administration of immunosuppressive drugs associated with significant potential toxicity
Outcomes	Major organ system dysfunction, opportunistic infection, mortality because of drug toxicity

search was initially limited to randomized controlled trials (RCTs), but because of the paucity of data for some drugs, the literature search was expanded to include prospective studies, case series, and systematic reviews. Case reports were also reviewed but not included in any of the evidence tables. The search strategy linked each drug with the key questions presented in Table 1 and restricted the search to patients with lung disease and lung transplant recipients. To locate studies such as systematic reviews and meta-analyses, the key words were used in Medline and the Cochrane Review databases. The ACCP clinical research analyst conducted an initial review of >500 abstracts. More than 350 full articles were formally reviewed and abstracted by the clinical research analyst, and >250 studies were included in the evidence tables. RCTs were scored using the Jadad et al¹ grading system. This system follows a method that is based on a three-point scale that rates randomization (and appropriateness), blinding (and appropriateness), and tracking of withdrawals and losses to follow-up. Studies were graded on a scale of 0 to 5. Study adequacy was then given a score from poor to excellent. Other prospective studies were informally graded on methodology and tracking of patients included in the studies. No formal quantitative analysis was performed because of the wide variety of studies included for each drug. Given the length of time required to prepare the final manuscript after conclusion of the systematic review, the panel included references in the text that were outside the formal review deadline to keep the guideline current. The evidence tables provide a summary of studies performed with individual drugs for organ transplantation and lung disease. These tables became the basis for the specific evidence-based recommendations regarding monitoring. Because of the paucity of evidence for the use of these drugs in lung transplantation, recommendations were based primarily on extrapolated data from other organ transplant studies.

2.2 Strength of Evidence and Grading of Recommendations

The ACCP system for grading guideline recommendations is based on the relationship between the strength of evidence and the balance of benefits to risk and burden (Table 3). Simply stated, recommendations can be strong (grade 1) or weak (grade 2). If there is certainty that the benefits do (or do not) outweigh risk, the recommendation is strong. If there is less certainty or the benefits and risks are more equally balanced, the recommendation is weaker. Several important issues must be considered when classifying recommendations. These include the quality of the evidence that supports estimates of benefit, risks, and costs; the importance of the outcomes of the intervention; the magnitude and precision of the estimate of treatment effect; the risks and burdens of an intended therapy; the risk of the target event; and varying patient values. The benefit-to-harm ratio includes consideration of the clinical improvements in health and quality of life as well as the burdens, risks, and costs, when applicable, identifiable, and determinable (Table 3). Patient and community values are important considerations in clinical decision-making and are factored into the grading process. In situations where the benefits clearly do or do not outweigh the risks, it is assumed that nearly all patients would have the same preferences. For weaker recommendations, however, there may not be consistency in patient preferences.

Quality of evidence is the second dimension of the grading chart. The strength of evidence is classified into three categories of high (Grade A), moderate (Grade B), and low or very low (Grade C) based on the quality of data. The highest-quality evidence comes from well-designed RCTs yielding consistent and directly applicable results. In some circumstances, high-quality evidence can be the result of overwhelming evidence from observational studies. Moderate-quality evidence is based on RCTs with some limitations that may include methodologic flaws or inconsistent results. Studies other than RCTs that may yield strong results are also included in the moderate category. The weakest evidence comes from other types of observational studies. It should be noted that the HSP endorses the principle that most relevant clinical studies provide evidence, although the quality of that evidence may vary. The minimum threshold for qualifying evidence, per HSP policy, is that it must be published in peer-reviewed journals. The balance of benefits to risk and burden and the level of certainty based on this balance are summarized in Table 4.

Table 3—Relationship of Strength of the Supporting Evidence to the Balance of Benefits to Risks/Burdens

Strength of Evidence		Balance of Benefits to Risks/Burdens		
Benefits Outweigh Risks/Burdens		Risks/Burdens Outweigh Benefits	Evenly Balanced	Uncertain
High		1A	1A	2A
Moderate		1B	1B	2B
Low or very low		1C	1C	2C

1A = strong recommendation; 1B = strong recommendation; 1C = strong recommendation; 2A = weak recommendation; 2B = weak recommendation; 2C = weak recommendation.

3.0 MONITORING OF NONSTEROIDAL IMMUNOSUPPRESSIVE DRUGS

A total of 20 nonsteroidal immunosuppressive drugs are reviewed in this guideline. A summary of evidence supporting the monitoring of nonsteroidal immunosuppressive drugs in patients with lung disease and lung transplant recipients is provided in evidence tables throughout these guidelines. For each drug, its toxicity, monitoring protocol, pregnancy classification, and recommendations are summarized in the following subsections organized by drug classification.

3.1 Anti-Tumor Necrosis Factor- α Agents

3.1.1 Adalimumab: The biologic agent adalimumab has been available in the United States for treatment of various conditions since 1997. It has been approved by the FDA for the treatment of rheumatoid arthritis²⁻⁵; psoriasis, including psoriatic arthritis⁶⁻⁸; ankylosing spondylitis^{9,10}; and Crohn's disease.^{11,12} There have been a limited number of case reports and one case series reporting on the utility of adalimumab for sarcoidosis.¹³⁻¹⁷ To date, there are no reports of using the drug for other pulmonary conditions, such as asthma. Table 5 summarizes clinical studies on the toxicity and monitoring of adalimumab in patients with various diseases.^{2,4,11,12,15,18}

3.1.1.1 Toxicity—Injection site reactions have been noted in about 20% of patients receiving adalimumab.^{11,12,18} In one series of patients with sarcoidosis, three of 27 developed injection site pain¹⁵; however,

no patient had discontinued the drug because of the reaction.

Serious infections have been associated with the use of adalimumab.^{4,11,18} However, in RCTs, the rate of serious infection was not statistically different from that encountered in the comparator group.^{2,12} Patients treated with adalimumab often were receiving other immunosuppressants, which may have led or contributed to the infections. In addition, many of these patients had one or more comorbidity.¹⁹

Patients receiving anti-tumor necrosis factor (TNF) agents are particularly at risk for reactivation of *Mycobacterium tuberculosis*. The risk is much higher for infliximab than for etanercept.²⁰ The reported rate of cases for adalimumab has been lower, even though it has immunologic effects that are similar to infliximab.²¹ However, this may reflect the more-intensive screening performed prior to starting adalimumab and use of isoniazid prophylaxis in patients at risk for reactivation of TB. In one prospective study of 531 patients treated with adalimumab, 30 were identified as high risk for *M tuberculosis*, and all received prophylactic therapy (mostly isoniazid). In that series, one patient developed TB, but she had a negative chest radiograph at the time of initiating adalimumab and did not receive anti-TB prophylaxis.² Other studies reported reactivation of TB while receiving isoniazid in patients treated with adalimumab.^{21,22} A retrospective study of 613 patients treated with any one of the three anti-TNF agents (202 received etanercept, 298 received infliximab, and 113 received adalimumab) reported that 36 patients were at increased risk for TB and treated with appropriate prophylactic medications.²² Eleven of these patients developed TB, three while receiving adalimumab and eight while receiving infliximab. The diagnosis of TB can be made more rapidly with immunodiagnostic techniques.²³ Patients receiving routine immunosuppressives, including prednisone, may have a false-negative tuberculin skin test, but they will still respond to *M tuberculosis*-specific γ -interferon testing.²⁴ In that study, however, the use of anti-TNF therapy was associated with false-negative *M tuberculosis*-specific γ -interferon testing.

Table 4—Description of Balance of Benefits to Risks/Burdens Scale

Balance of Benefits	Risks/Burdens
Benefits clearly outweigh the burdens	Certainty of imbalance
Risks/burdens clearly outweigh the benefits	Certainty of imbalance
The risks/burdens and benefits are closely balanced	Less certainty
The balance of benefits to risks/burdens is uncertain	Uncertainty

Table 5—Monitoring of Adalimumab

Author/Year	Study Design	Disease	Comparator	Dose	No. Patients Treated	Duration of Therapy	Duration of Monitoring	Complications Noted	Study Adequacy ^a	Coadministered Agents	Comments
Heffernan and Smith ¹⁵ /2006	CR	Sarcoidosis	None	40 mg SQ weekly	1	10 wk	10 wk	None	2	HCQ	None
Baughman ¹⁹ /2007	CS	Sarcoidosis	None	40 mg SQ every 1-2 wk	27	Up to 3 y	Up to 3 y	Five (18.5%): Reactions at injections sites, 3 Infections, 2 None	3	Various	None
Marnane et al ¹⁷ /2009	CR	Neurosarcoidosis	None	40 mg SQ every other week	1	6 mo	2 y	None	4	None	None
Sandborn et al ¹² /2007	PRCT, DB, MC	Crohn's	Placebo	160 mg wk 0, 80 mg wk 2 SQ	325	4 wk	4 wk	No different from placebo Serious infections: A = 0, PI = 2% Injection site reaction: A = 11%, PI = 10% No malignancy	5	None	No long-term follow-up
Sandborn et al ¹¹ /2007	DB, MC, OL	Crohn's	Placebo	40 mg SQ every 1-2 wk	276	56 wk	56 wk	Nasopharyngitis, 19% Injection site reaction, 12% Malignancy, 1 patient No serious infection	5	None	Most problems reported in open-label follow up
Weinblatt et al ¹ /2006	OL	RA	None	20-80 mg SQ weekly	262	3.4 y	4 y	Serious infection, 2.03/100 patient-y Demyelinating disease, 1 patient Congestive heart failure, 1 patient	5	Prednisone MTX	None
Breedveld et al ² /2006	DB, MC, RT	RA	MTX A alone A + MTX	40 mg SQ every 2 wk	MTX = 268 A alone = 274 A + MTX = 257	2 y	2 y	Serious infection: MTX, 15.9% A alone, 21.1% A + MTX, 18.5% 1 patient with TB (A + MTX) Lupus-like reaction, 1 A-alone patient Ten cancers, no difference between groups	5	None	None

A = adalimumab; CR = case report; CS = case series; DB = double-blind; HCQ = hydroxychloroquine; MC = multicenter; MTX = methotrexate; OL = open label; PRCT = prospective, randomized controlled trial; PS = prospective study; RA = rheumatoid arthritis; RS = retrospective series; SC = single center; SQ = subcutaneous.

^aStudy adequacy 0 to 5 (poor to excellent).

Adalimumab has been associated with a cluster of cases of *Legionella pneumophila* pneumonia.²⁵ There are also case reports of adalimumab-treated patients developing *Pneumocystis jirovecii* pneumonia²⁶ and atypical mycobacteria.²⁷

In clinical trials, the overall rate of serious infections appears similar to the comparator groups.^{2,12} For 262 patients treated for a mean of 3.4 years, the rate of serious infections was 2.03 per 100 patient-years.⁴ In evaluating a data bank of 16,788 patients with rheumatoid arthritis, adalimumab was not associated with an increased rate of hospitalization for pneumonia.²⁸ The use of prednisone was associated with the highest risk.

Autoimmune disease appears to be induced by anti-TNF agents.²⁹ In a detailed analysis of the cases reported to date, Ramos-Casals et al²⁹ identified 92 cases of a lupus-like reaction, including 15 patients treated with adalimumab. Vasculitis was reported in 113 patients, including five treated with adalimumab.

Pulmonary fibrosis as either a new event or an exacerbation of underlying fibrosis has been reported in patients treated with adalimumab.³⁰⁻³² Overall, interstitial pneumonias have been reported in at least 18 patients receiving various anti-TNF agents.²⁹

Sarcoidosis also has been reported in patients treated with anti-TNF agents.^{29,33} The mechanism is unclear.³⁴

The risk for malignancy for patients receiving anti-TNF agents remains unclear. CNS events, including demyelination disorders, have been sporadically reported in patients treated with adalimumab.^{35,36}

3.1.1.2 Pregnancy Classification—No adequate, well-controlled studies of adalimumab administered to pregnant women exist. The FDA has designated adalimumab as category B for all trimesters.³⁷ There appears to be an increased rate of first trimester miscarriages with the agent, although there have been a few successful pregnancies for women receiving adalimumab.³⁸ There are insufficient data to establish its safety in breast-feeding.³⁷

3.1.1.3 Monitoring—There is an increased risk of reactivation of hepatitis B and TB. If there are symptoms or signs of these infections, diagnosis of specific infection can be made using standard techniques.³⁹ Anti-double-stranded DNA antibodies can be measured if lupus-like symptoms develop during therapy.³⁷

Considerations for clinicians regarding adalimumab for patients with lung disease and lung transplant recipients:

- *Assessing risk for TB:* Tuberculin skin testing and a chest radiograph should be obtained and reviewed prior to therapy. In addition, one

should consider the risk for histoplasmosis, blastomycosis, or coccidiomycosis for patients living in or visiting endemic areas.

- *Assessing risk for hepatitis:* Hepatitis serology should be obtained prior to onset of therapy. Use of etanercept should be avoided if active viral hepatitis is present.
- *Monitoring blood work:* Patients with a history of viral hepatitis or chronic carrier states should be monitored for viral hepatitis reactivation as long as they are on therapy.
- *Monitoring of drug clearance:* This is not applicable.
- *Monitoring for drug/drug interaction:* Live vaccines should be avoided while patients are being treated with adalimumab.
- *Prophylaxis against infections:* No specific recommendations are available.

The following topics have been identified for prioritization for future research regarding adalimumab:

- *The need for infection prophylaxis.*
- *The risk for reactivation of latent infection (eg, TB, histoplasmosis).*
- *The risk of malignancy.*
- *The appropriate strategy for monitoring for infection.*
- *The risk of heart disease exacerbation in patients with congestive heart failure (CHF).*

Information for patients:

- *Check your temperature frequently and report a fever to your physician immediately.*
- *Report to your physician signs of infection, such as cough, aches, fever, and chills; a wound or cut with redness, pain, discharge, or pus; pain; burning with urination; and nausea; vomiting; and diarrhea.*
- *Report shortness of breath or other changes in your breathing to your physician.*

3.1.2 Etanercept: Etanercept has regulatory approval for treatment of rheumatoid arthritis,⁴⁰⁻⁴³ psoriasis,^{40,44-47} juvenile rheumatoid arthritis,^{40,48} and ankylosing spondylitis.^{40,49-51} No reports of large, randomized, prospective clinical trials of etanercept for treatment of inflammatory lung disease have appeared in the literature, although a phase 2 trial for the treatment of idiopathic pulmonary fibrosis (IPF) has been completed and published after this analysis was completed.⁵² Table 6 summarizes the clinical trials for sarcoidosis^{53,54} and granulomatosis with polyangiitis⁵⁵ as well as five large trials in nonpulmonary

indications, which provide information regarding drug toxicity.^{41,43,44,49,51}

3.1.2.1 Toxicity—Patients with chronic hepatitis B virus (HBV) infection or chronic HBV carriers (positive for surface antigen) are at risk for HBV reactivation,³⁹ and active HBV infections have been reported in patients receiving etanercept. Reactivation of HBV has typically occurred with concomitant use of other immunomodulatory agents; it has responded to withdrawal of the TNF antagonist, addition of antiviral therapy, or both. The most noteworthy adverse effects that have been associated with etanercept include injection site reactions, allergic reactions,⁴⁰ opportunistic infections such as TB,⁵⁶ CHF,⁵⁷ leukocytoclastic vasculitis,⁵⁸ a syndrome resembling lupus erythematosus,⁵⁹⁻⁶¹ and CNS demyelination.^{40,62} Other possible toxicities include diabetic ketoacidosis,⁶³ hyperthyroidism,⁶⁴ thyroiditis,⁶⁵ GI dysfunction (vomiting, abdominal pain, and cholecystitis),^{40,66} blood dyscrasias (anemia, leukopenia, neutropenia, pancytopenia, thrombocytopenia, hemophagocytic syndrome),^{40,66,67} septic arthritis,⁶⁸ optic neuritis,⁶⁹ cough,^{40,70} viral pneumonia,⁷¹ and lymphoma.⁴⁰ In general, most of these toxicities are associations based on case reports or reports to the FDA Adverse Event Reporting System; the strength of association for many of them is extremely weak. A very rare syndrome of granulomatous pulmonary inflammation that resembles sarcoidosis has also been reported.^{72,73} Serious injection site reactions can occur,⁴⁰ and injection site-associated necrotizing fasciitis has been reported.⁷⁴ Although seen in up to 37% of individuals, most reactions are mild to moderate.

Infection risk is increased when etanercept is given concurrently with other immunosuppressants.⁴⁰ Reactivation of latent TB has been associated with TNF inhibitors,⁷⁵ but it is unclear whether etanercept therapy increases the risk above the already increased risk of reactivation TB for patients with rheumatoid arthritis.⁵⁶ In the available case series, TB infection was extrapulmonary in one-half of the cases, suggesting that etanercept increases the risk for reactivation TB.⁵⁶ The soluble TNF fusion receptors seem to be associated with less risk of reactivation TB than the monoclonal TNF antagonists infliximab and adalimumab.⁷⁵ Other infections that have been reported in patients treated with etanercept in postmarketing studies include endemic fungi, atypical mycobacteria, candidiasis, aspergillosis, cytomegalovirus, herpes zoster, *Pneumocystis*, and *Listeria monocytogenes*.

There has been substantial controversy regarding the use of TNF antagonists in patients with cardiomyopathy, resulting in a black box warning from the FDA for infliximab use in patients with New York Heart Association class III to IV symptoms.⁷⁶ However, this effect has not been convincingly linked

to etanercept therapy.^{77,78} As a treatment of established heart failure, etanercept was studied in two large trials that showed no benefit and no clear indication of the increased mortality seen with infliximab, which has a different mechanism of action. However, there have been subsequent case reports of de novo cardiac failure or worsening of preexisting cardiac dysfunction in patients treated with etanercept.⁵⁷

There have been postmarketing surveillance reports of non-Hodgkin's lymphoma in patients treated with etanercept, including several cases where the lymphoma regressed following cessation of the drug.^{53,79} However, the baseline incidence of lymphoma is increased in individuals with the chronic inflammatory diseases that are treated with etanercept. The largest study to date that addressed this issue was in rheumatoid arthritis and did not demonstrate a statistically significant increased incidence in individuals receiving etanercept.⁸⁰ Other malignancies do not appear to be more frequent in etanercept-treated individuals.

The data suggesting that etanercept is associated with increased risk of de novo demyelinating syndromes do not demonstrate an incidence above the baseline population rate (FDA briefing document). However, there are well-described cases of new demyelination in patients with preexisting multiple sclerosis who are treated with lenercept, a similar TNF antagonist fusion protein (Lenercept Multiple Sclerosis Study Group). Optic neuritis, transverse myelitis, and Guillain-Barré syndrome have all been observed in postmarketing reports.

3.1.2.2 Pregnancy Classification—The safety of etanercept has not been established during pregnancy, and it has been designated as category B by the FDA for all trimesters.⁴⁰ There are insufficient clinical data to confirm its safety in breast-feeding.⁴⁰

3.1.2.3 Monitoring—There is no known role for routine monitoring for antinuclear antibody formation or anti-tanercept antibodies. Although these develop in up to 11% and 2% of patients, respectively, they rarely influenced efficacy of the medication or led to overt autoimmune disease during short- to medium-duration use.⁸¹

Considerations for clinicians regarding etanercept for patients with lung disease and lung transplant recipients:

- **Assessing risk for TB:** Tuberculin skin testing and a chest radiograph should be obtained and reviewed prior to therapy. In addition, one should consider the risk for histoplasmosis, blastomycosis, or coccidiomycosis for patients living in or visiting endemic areas.

Table 6—Monitoring of Etanercept

Author/Year	Study Design	Disease	Dose ^a	No. Patients Treated	Age, y	Duration of Therapy	Monitoring Used	Complications Noted	Study Adequacy	Coadministered Agents	Comments
Keystone et al ¹⁴ /2004	PRCT, DB, MC	RA	50 mg once weekly (n = 214), 25 mg twice weekly (n = 153)	ETAN: 367; placebo: 53	≥ 20	≥ 16 wk	Clinical evaluation	Injection site reactions, nausea	4	MTX, corticosteroids, NSAIDs	Placebo group switched to ETAN at 8 wk
van der Heijde et al ¹⁵ /2006	PRCT, DB, PC, MC	RA	25 mg twice weekly	686	≥ 18	≥ 2 y	Clinical evaluation	Injection site reactions, hypertension	5	MTX (1 of 3 arms)	Study consisted of three cohorts (ETAN, MTX, ETAN + MTX); no increased malignancy risk
Leonardi et al ¹⁶ /2003	PRCT, PC, DB, MC	Psoriasis	Low ETAN (25 mg once weekly), medium ETAN (25 mg twice weekly), high ETAN (50 mg twice weekly)	Low-dose ETAN: 160; medium-dose ETAN: 162; high-dose ETAN: 164	45.1	24 wk	Clinical evaluation	Injection site reactions	4	None stated	No withdrawals because of abnormal laboratory test values
Davis et al ¹⁷ /2003	PRCT, PC, DB, MC	Ankylosing spondylitis	25 mg twice weekly	ETAN: 138; placebo: 139	18-70	24 wk	Clinical evaluation	Injection site reactions	4	± DMARD	URI and accidental injury occurred more frequently in ETAN group
Calin et al ¹⁸ /2004	PRCT, PC, DB, MC	Ankylosing spondylitis	25 mg twice weekly	ETAN: 45; placebo: 39	18-70	12 wk	Clinical evaluation	Injection site reactions	3	± DMARD	No study drug discontinuations for safety reasons
Baughman et al ¹⁹ /2005	PRCT, DB, PC, SC	Ocular sarcoidosis	25 mg twice weekly	18	Not stated	≥ 6 mo	Clinical evaluation, ocular examination	No serious adverse events noted	2	MTX; corticosteroids	None or NR
Seo et al ²⁰ /2005	PRCT, DB, PC, MC	Granulomatosis with polyangiitis	25 mg twice weekly	ETAN: 89; placebo: 91	52 ± 14	12 mo	Clinical evaluation	Incidence of cytopenias, infection, congestive heart failure, or venous thrombosis similar in ETAN vs placebo groups	4	Corticosteroids; MTX (limited disease CYC (severe disease))	Severe and total adverse events similar for ETAN vs placebo groups; solid cancer incidence increased in ETAN vs placebo groups
Utz et al ²¹ /2003	PS, OL	Pulmonary sarcoidosis	25 mg twice weekly	17	35-74	3-15 mo	Clinical evaluation, BAL, PFT	GI lymphoma (1), nasopharyngeal extramedullary plasmacytoma (1)	1	None or NR	None or NR

CYC = cyclophosphamide; DMARD = disease-modifying antirheumatic drug; ETAN = etanercept; NR = not reported; NSAID = nonsteroidal antiinflammatory drug; PC = placebo controlled; PFT = pulmonary function test; OS = observational study; URI = upper-respiratory infection. See Table 5 legend for expansion of other abbreviations.
^aAll studies used subcutaneous administration.

- *Assessing risk for hepatitis:* Hepatitis serology should be obtained prior to onset of therapy. Use of etanercept should be avoided if active viral hepatitis is present.
- *Monitoring blood work:* Patients with a history of viral hepatitis or chronic carrier states should be monitored for viral hepatitis reactivation as long as patients are on therapy.
- *Monitoring of drug clearance:* This is not applicable.
- *Monitoring for drug/drug interaction:* Live vaccines should be avoided while patients are being treated with etanercept.
- *Prophylaxis against infections:* No specific recommendations are available.

The following topics have been identified for prioritization for future research regarding etanercept:

- *The need for infection prophylaxis.*
- *The risk for reactivation of latent infection (eg, TB, histoplasmosis).*
- *The risk of malignancy.*
- *The appropriate strategy for monitoring for infection.*
- *The risk of heart disease exacerbation in patients with CHF.*

Information for patients:

- *Check your temperature frequently and report a fever to your physician immediately.*
- *Report to your physician signs of infection, such as cough, aches, fever, and chills; a wound or cut with redness, pain, discharge, or pus; pain; burning with urination; and nausea, vomiting, and diarrhea.*
- *Report shortness of breath or other changes in your breathing to your physician.*

3.1.3 Infliximab: Infliximab has regulatory approval for the treatment of refractory rheumatoid arthritis, psoriasis, ankylosing spondylitis, ulcerative colitis, and Crohn's disease.⁸² Infliximab has been used in corticosteroid refractory pulmonary and extrapulmonary sarcoidosis, asthma, COPD, and anorexia associated with lung cancer.⁸³⁻⁹⁰ Table 7 summarizes the use of infliximab for lung disease, including four RCTs for lung disease^{86,89,91,92} and 11 case series of infliximab in which additional information regarding toxicity is provided.^{85,93-102} Also included in Table 8 are several studies in nonpulmonary disease that provide specific information regarding toxicity of the drug.^{10,76,103-135}

3.1.3.1 Toxicity—Detailed reviews of the side effect profile have been published.³⁵ Infections are the most common adverse events reported with the use of infliximab.¹³⁶ Although the data are confounded by

a baseline increase in infections in patients treated with infliximab, the risk of infection may be increased by approximately twofold.¹³⁶ Most infections have been upper-respiratory tract or urinary tract infections, and these have not been serious.³⁵ Case-control studies suggest an increased incidence of opportunistic infections.³⁵ Ledingham et al¹³⁷ suggested that anti-TNF therapy not be started in the presence of infection and should be discontinued in the presence of serious infection.

Data regarding TB infection are the best developed. A series of case reports from California was reported¹³⁸ and subsequently expanded on in follow-up reports.¹³⁹ Although no prospective, randomized data exist, reports suggest that the rate of TB development may be greater with infliximab than other anti-TNF agents,^{20,140} but differences in reporting and use worldwide make this difficult to determine.¹⁴¹ It also appears that there is a greater likelihood of extrapulmonary involvement in these patients.¹³⁸⁻¹⁴¹ In addition, one-half of reported cases was diagnosed after three or more infusions^{20,138,139} in a median of 12 weeks, which suggests reactivation disease.^{20,140}

There are insufficient data to determine whether lymphoma or nonlymphomatous malignancies are increased as a result of using infliximab, particularly in populations other than those with rheumatoid arthritis.³⁵ Hepatosplenic T-cell lymphomas have been reported in few postmarketing studies, particularly in adolescent and young adult patients with Crohn's disease. All these cases have occurred in patients receiving concomitant treatment with azathioprine or 6-mercaptopurine. Ledingham et al¹³⁷ suggested that caution be exercised in the use of infliximab in patients with a history of malignancy.

A large placebo-controlled trial of infliximab (5 or 10 mg/kg) was completed in patients with New York Heart Association class III or IV heart failure (ATTACH [Anti-TNF Therapy Against Congestive Heart Failure] trial).⁷⁶ There was no benefit, and the risk of all causes of death or hospitalization for heart failure was increased in the infliximab-treated (10 mg/kg) patients. Furthermore, there have been numerous postmarketing reports of worsening heart failure during therapy.³⁵ CNS events, including demyelination disorders, have been reported sporadically with agents that inhibit TNF- α ,³⁵ although they may occur with lesser frequency with infliximab.¹⁴²

Rare cases of systemic lupus erythematosus-like syndromes have been reported with anti-TNF therapy and generally resolved within 6 weeks to 14 months of discontinuation of the drug.¹³⁷ The incidence of lupus is lower than the incidence of developing antinuclear antibodies.³⁵

Rare reports of hematologic side effects have been noted, including leukopenia, neutropenia,

Table 7—Monitoring of Infliximab for Lung Disease

Author/Year	Study Design	Disease	Dose ^a	Route	No. Patients Treated	Age, y	Duration of Therapy	Duration of Monitoring	Complications Noted	Study Adequacy	Comments Malignancy/Death Pregnancy
RCT											
van der Vaart et al ⁶⁹ /2005	SC, DB, PCRT	COPD	5 mg/kg	IV	22	NR	6 wk	9 wk	Cough more frequent with infliximab, 8 vs 0 subjects	3	None
Erin et al ⁶² /2006	DB, PRCT	Asthma	5 mg/kg	IV	38	19-66	6 wk	12 wk	Fewer asthma exacerbations in infliximab arm ($P = .01$)	4	One patient died in parachute accident in infliximab arm
Baughman et al ⁸⁰ /2006	DB, PRCT	Sarcoidosis	3 mg/kg or 5 mg/kg on weeks 0, 2, 6, 12, 18, 24	IV	138	NR	24 wk	52 wk	More serious pneumonia in infliximab (4.4%) than placebo (0%)	4	Two cancers in infliximab group (one fatal)
Remnard et al ⁸⁹ /2007	DB, PRCT	COPD	3 mg/kg or 5 mg/kg weeks 0, 2, 6, 12, 18, 24	IV	234	NR	24 wk	44 wk	More pneumonia in infliximab than placebo (10 vs 1); more infusion reactions in infliximab (10% vs 4%) and delayed hypersensitivity reactions (4% vs 0%)	4	More malignancies overall in infliximab (n = 12) vs placebo (n = 3)
Other studies											
Yee and Pochapin ⁶³ /2001	OLT	Sarcoidosis	5 mg/kg at 0, 2, and 6 wk	IV	1 (lymph node, abdominal)	72	6 wk	6 wk	None	0	None
Petersen et al ⁶⁴ /2002	OLT	Sarcoidosis	5 mg/kg at 0, 2, and 6 wk and every 2 mo	IV	1 (neurologic indication for therapy)	46	6 mo	6 mo	None	0	None
Ullricht et al ⁶⁵ /2003	OLT	Sarcoidosis	3 mg/kg at 0, 2, and 6 wk and every 8 wk	IV	1 (hepatic/arthritis)	51	10 mo	10 mo	None	0	None
Roberts et al ⁶⁷ /2003	OLT	Sarcoidosis	5 mg/kg at baseline, 2, 4, and 8 wk and every 2 mo	IV	1	50	NA	NA	None	0	None
Katz et al ⁶⁸ /2003	OLT	Sarcoidosis	3 mg/kg at time 0, 10 mo later, and monthly thereafter	IV	1 (optic)	35	13 mo	13 mo	None	0	None

(Continued)

Table 7—Continued

Author/Year	Study Design	Disease	Dose ^a	Route	No. Patients Treated	Age, y	Duration of Therapy	Duration of Monitoring	Complications Noted	Study Adequacy	Comments
Meyerle and Shorr ⁹⁸ /2003	OLT	Sarcoidosis	5 mg/kg at 0, 2, 4, and 12 wk	IV	1 (skin)	37	12 wk	12 wk	None	0	None
Jatoi et al ¹⁰¹ /2004	OLT	Non-small cell lung cancer with anorexia treated with docetaxel	5 mg/kg on weeks 1, 3, and 5 and every 4 wk	IV	4	67-77	33-125 d	33-125 d	No grade 4 or 5 toxicities in any patient ^b	2	<i>Clostridium difficile</i> in one patient
Pritchard and Nadarajah ¹⁰² /2004	OLT	Sarcoidosis	3 mg/kg at 0, 2, and 6 wk and every 4-8 wk	IV	5 patients (2 eye, 1 neuro, 1 pulmonary, 1 abdominal)	31-74	NA	NA	None	1	None
Haley et al ¹⁰⁰ /2004	OLT	Sarcoidosis	5 mg/kg at 0, 2, and 6 wk	IV	1 (skin)	39	6 wk	6 wk	None	0	None
Ali and Perlman ⁹⁹ /2004	OLT	Sarcoidosis	5 mg/kg every 6 mo	IV	1 (eye)	NA	6 mo	6 mo	None	0	None
Doty et al ⁹⁵ /2005	OLT	Sarcoidosis	3-5 mg/kg at various schedules	IV	10 (6 skin, 2 lung, 1 adenopathy, 1 muscle)	16-44	6-128 wk	Up to 128 wk	One anaphylactic reaction	0	One malignancy

NA = not available; NS = nonsignificant; OLT = open-label trial. See Table 5 and 6 legends for expansion of other abbreviations.

^aDose administered at time 0, 2 wk, 64 wk, and every 4 wk thereafter, unless otherwise noted.

^bToxicities measured by the 5-point scale of the National Cancer Institute Common Toxicity Criteria, version 2 (http://www.eortc.be/services/doc/ctc/ctcv20_4-30-992.pdf).

Table 8—Monitoring of Infliximab for Other Diseases

Author/Year	Study Design	Disease	Dose ^a	Route	No. Patients Treated	Age, y	Duration of Therapy	Duration of Monitoring	Complications Noted	Study Adequacy	Comments Malignancy/Death Pregnancy
Elliott et al ¹⁰³ /1994	DB, PRCT 3 arms	RA	1 mg/kg or 10 mg/kg	IV	73	NR	Single dose	4 wk	One pneumonia in 1 mg/kg group	5	None
Maini et al ¹⁰⁴ /1998	DB, PRCT 7 arms	RA on MTX	1, 3, or 10 mg/kg at baseline and 2, 6, 10, and 14 wk and MTX 7.5 mg weekly or placebo	IV	101	NR	14 wk	26 wk	Two serious infections in infliximab + MTX groups	4	One fatal infection in infliximab + MTX groups
Maini et al ¹⁰⁵ /1999	DB, PRCT 5 arms	RA on MTX	3 mg/kg or 10 mg/kg at baseline and 2 and 6 wk and every 4 or 6 wk thereafter	IV	428	19-80	30 wk	30 wk	Any infection incidence higher in 10 mg/kg groups	4	Three malignancies in 10 mg/kg every 4 wk group, two infliximab and three placebo deaths
Present et al ¹⁰⁶ /1999	DB, PRCT 3 arms	Fistulizing Crohn's disease	3 mg/kg or 10 mg/kg at baseline and 2 and 6 wk and every 4 or 6 wk thereafter	IV	94	NR	6 wk	34 wk	Trend to more AEs and SAEs with 10 mg/kg	4	None
Lipsky et al ¹⁰⁷ /2000	DB, PRCT 5 arms	RA on MTX	3 mg/kg or 10 mg/kg at baseline and 2 and 6 wk and every 4 or 8 wk thereafter	IV	428	NR	54 wk	54 wk	Overall SAEs and infections similar between infliximab and placebo groups	4	Five malignancies in infliximab groups, three deaths in MTX-alone group and five in MTX + infliximab groups
Chaudhari et al ¹⁰⁸ /2001	DB, PRCT 3 arms	Psoriatic arthritis	5 mg/kg or 10 mg/kg at baseline and 2 and 6 wk; OL 5 mg or 10 mg in placebo at 10, 12, and 16 wk	IV	33	27-68	10 wk in primary analysis; 16 wk in secondary analysis	10 wk in primary analysis	More headaches in 10 mg/kg group	5	None

(Continued)

Table 8—Continued

Author/Year	Study Design	Disease	Dose ^a	Route	No. Patients Treated	Age, y	Duration of Therapy	Duration of Monitoring	Complications Noted	Study Adequacy	Comments Malignancy/Death Pregnancy
Van den Bosch et al ^{11/2002}	DB, PRCT, SC 2 arms	Spondyloarthropathy	5 mg/kg at baseline and 2 and 6 wk	IV	40	29-66	6 wk	12 wk	TB in one; four new ANAs in active group	4	None
Braun et al ^{10/2002}	DB, PRCT 2 arms	Ankylosing spondylitis	5 mg/kg at 0, 2, and 6 wk	IV	70	NR	6 wk	12 wk	One extrapulmonary TB and one bronchiocentric allergic granulomatosis in infliximab group	5	None
Hanauer et al ^{10/2002}	DB, PRCT 3 arms	Crohn's disease	5 mg/kg to all followed by placebo or 5 mg/kg at 2 and 6 wk and every 8 wk thereafter or 5 mg/kg at 2 and 6 wk followed by 10 mg/kg every 8 wk; after 14 wk, initial responders could cross to 5, 10, or 15 mg/kg	IV	573	27-46	46 wk	54 wk	One TB at week 14; serious infections similar among all groups	4	Three deaths in multiple infusion groups, six malignancies
Chung et al ^{10/2003}	DB, PRCT 3 arms	Congestive heart failure	5 mg/kg or 10 mg/kg at baseline and 2 and 6 wk	IV	150	NR	6 wk	28 wk	Increased worsening clinical status (death or hospitalization) and SAEs in 10 mg/kg group	3	Three deaths in 10 mg/kg, 1 in 5 mg/kg, none in placebo during 28 wk of follow-up
Durez et al ^{13/2004}	PRCT 2 arms	RA on MTX	Methylprednisolone 1 g at 0 wk vs infliximab 3 mg/kg at 0, 2, and 6 wk	IV	27	34-79	6 wk	12 wk	No differences	2	None

(Continued)

Table 8—Continued

Author/Year	Study Design	Disease	Dose ^a	Route	No. Patients Treated	Age, y	Duration of Therapy	Duration of Monitoring	Complications Noted	Study Adequacy	Comments
St Clair et al ¹¹⁶ /2004	DB, PRCT 3 arms	RA	4:5:5 randomization to MTX/placebo; MTX + 3 mg/kg and MTX + 6 mg/kg; infliximab dosed at 0, 2, and 6 wk and every 8 wk	IV	1,049	NR	46 wk	54 wk	More SAEs and infections (pneumonias) in MTX + infliximab groups; four TB cases in infliximab groups	5	Four malignancies, all in MTX + 6 mg/kg group, four deaths (two in placebo group)
Mariette et al ¹¹⁴ /2004	DB, PRCT 2 arms	Sjögren syndrome	5 mg/kg at 0, 2, and 6 wk	IV	103	NR	6 wk	22 wk	Six of seven SAEs in infliximab group	5	One cancer in infliximab group
Maini et al ¹⁰⁵ /1999	OL extension, PRCT 5 arms	RA on MTX	3 mg/kg or 10 mg/kg every 4 or 8 wk	IV	216	NR	102 wk	102 wk	Any infection incidence higher in 10 mg/kg groups	4	One cancer in MTX-only and nine in infliximab groups; four deaths in MTX only and seven in infliximab groups
Sands et al ¹¹⁵ /2004	DB, PRCT 2 arms	Fistulizing Crohn's disease	5 mg/kg at 0, 2, and 6 wk; randomized to placebo or 5 mg/kg at 14, 22, 30, 38, and 46 wk	IV	306	NR	46 wk	54 wk	No difference in AEs	5	Two deaths in infliximab groups
Booth et al ¹¹² /2004	OL RCT	Antineutrophil cytoplasmic antibody-associated vasculitis	5 mg/kg at 0, 2, 6, and 10 wk; if remission, 5 mg/kg every 6 wk (study I) or azathioprine and prednisone maintenance (study II)	IV	32	NR	1 y	1 y	Two serious infections in study I; four serious infections in study II	1	Two deaths in study I and one lymphoma

(Continued)

Table 8—Continued

Author/Year	Study Design	Disease	Dose ^a	Route	No. Patients Treated	Age, y	Duration of Therapy	Duration of Monitoring	Complications Noted	Study Adequacy	Comments Malignancy/Death Pregnancy
Gokoop-Ruiterman et al ¹²⁰ /2007	DP, PRCT 4 arms	RA	MTX 25–30 mg/wk + 3 mg/kg for 3 wk then increased to 6 mg/kg if ineffective	IV	508	NR	12 mo	15 mo	AEs not different between groups	5	NR
van der Heijde et al ¹²¹ /2005	DB, PRCT 3:8 randomization to infliximab	Ankylosing spondylitis	5 mg/kg at baseline and 2, 6, 12, and 18 wk	IV	201	NR	18 wk	24 wk	More AEs in infliximab group (82.2%) than placebo (72.0%); seven vs two serious; more liver function abnormalities with infliximab	4	NR
Braun et al ¹¹⁸ /2005	OL phase of DB, PRCT	Ankylosing spondylitis	5 mg/kg every 6 wk in those previously on same dose or placebo	IV	54	NR	2 y	2 y	Six SAEs; three discontinued therapy as pregnancy planned	1	NR
Marzo-Ortega et al ¹²⁰ /2005	DB, PRCT 2 arms	Ankylosing spondylitis	5 mg/kg at 0, 2, 6, 14, and 22 wk	IV	42	28–74	22 wk	30 wk	No SAEs	3	NR
Reich et al ¹²¹ /2005	DB, PRCT 3 arms; 4:1 randomization	Psoriasis	5 mg/kg at 0, 2, and 6 wk then every 8 wk; placebo patients crossed over at 24 wk and received 5 mg/kg every 8 wk	IV	378	NR	46 wk	50 wk	Slightly higher AEs (82%) in infliximab compared with placebo (71%) through week 24; three serious infections in infliximab-treated patients	5	None

(Continued)

Table 8—Continued

Author/Year	Study Design	Disease	Dose ^a	Route	No. Patients Treated	Age, y	Duration of Therapy	Duration of Monitoring	Complications Noted	Study Adequacy	Comments
Rutgeerts et al ²² /2005	DB, PRCT 3 arms	Ulcerative colitis	5 or 10 mg/kg at 0, 2, and 6 wk and every 8 wk for 46 wk (ACT 1) or week 22 (ACT 2)	IV	364 (ACT 1) 364 (ACT 2)	NR	46 wk (ACT 1) 22 wk (ACT 2)	54 wk (ACT 1) 30 wk (ACT 2)	Similar adverse and SAEs as placebo; three neurologic adverse events in infliximab arms of both studies; one TB case in infliximab arm of ACT 1	5	Three malignancies in 5 mg/kg ACT 1 arm, one malignancy in the 5 mg/kg arm and one in the placebo arm of ACT 2
Korhonen et al ¹⁹ /2005	DB, PRCT 2 arms	Disc herniation-induced sciatica RA on MTX	5 mg/kg single dose	IV	40	NR	Single dose	12 wk	NR	5	None
Taylor et al ²⁸ /2006			5 mg/kg at 0, 2, and 6 wk and every 8 wk until 46 wk then placebo infusion at 56 wk and 5 mg/kg every 8 wk thereafter; initial placebo group received 5 mg/kg at 54, 56, and 62 wk and every 8 wk thereafter	IV	24	NR	110 wk	110 wk	NR	3	None

(Continued)

Table 8—Continued

Author/Year	Study Design	Disease	Dose ^a	Route	No. Patients Treated	Age, y	Duration of Therapy	Duration of Monitoring	Complications Noted	Study Adequacy	Comments
Westhovens et al ²⁹ /2006	DB, PRCT 3 arms	RA on MTX	3 mg/kg (group 2) or 10 mg/kg (group 3) at 0, 2, 6, and 14 wk; after 22 wk, placebo patients crossed to 3 mg/kg at 22, 26, and 30 wk and every 8 wk; after 22 wk, group 2 continued on 3 mg/kg every 8 wk; group 3 continued 10 kg/kg every 8 wk	IV	1,084	43-61	46 wk	54 wk	Increased risk of infections in group 3 (mostly pneumonias); nine TB cases (four in group 3)	5	Five total deaths; 26 patients with cancer (seven in the placebo group)
Abe et al ²⁴ /2006	DB, PRCT 3 arms	RA on MTX	3 mg/kg or 10 mg/kg at 0, 2, and 6 wk followed by OLT of 3 mg/kg every 8 wk	IV	147	20-75	14 wk randomized 36 wk OLT	36 wk	No difference in AEs between groups	4	Two deaths in the 10 mg/kg group
Lémann et al ²⁷ /2006	DB, PRCT 3 arms	Crohn's disease on azathioprine or 6-mercaptopurine	5 mg/kg at 0, 2, and 6 wk	IV	115	22-38	6 wk	24 wk	No difference in AEs or infections	4	None
Kavanaugh et al ³² /2007	DB, PRCT	Psoriatic arthritis	5 mg/kg 0, 2, 6, 14, and 22 wk, then all crossed over to active drug through 54 wk; 15 patients continued on 10 mg/kg after 38 wk, 45%-47% on MTX	IV	200	NR	54 wk	54 wk	No difference in AEs or SAEs	5	Two cancers (one in placebo and one in infliximab groups)

(Continued)

Table 8—Continued

Author/Year	Study Design	Disease	Dose ^a	Route	No. Patients Treated	Age, y	Duration of Therapy	Duration of Monitoring	Complications Noted	Study Adequacy	Comments Malignancy/Death Pregnancy
Gokoop-Ruiterman et al ³⁹ /2007	RCT 4 arms; follow-up of Be ST study	Early RA	MTX followed by sequential monotherapy (group 1); MTX followed by sequential combination therapy, including infliximab (group 2); combination followed by tapered steroids (group 3); initial combination with infliximab (group 4)	IV for infliximab	508	NR	2 y	2 y	Two TB cases with one death in group 4	3	Two cancers in group 1, one cancer and one death in group 2, one cancer/death in group 3, and one cancer and two deaths in group 4
Salvarani et al ³³ /2007	DB, PRCT 2 arms	Polymyalgia rheumatica on prednisone	3 mg/kg at 0, 2, 6, 14, and 22 wk	IV	51	NR	22 wk	52 wk	No difference in SAEs; one infliximab patient withdrew because of infection	5	One cancer in placebo group
Hoffman et al ¹⁷ /2007	DB, PRCT 2 arms	Giant cell arteritis	2:1 randomization to 5 mg/kg at 0, 2, and 6 wk and every 8 wk	IV	44	NR	54 wk	54 wk	No difference in SAEs; more patients in infliximab group discontinued treatment early	5	One cancer in placebo group
Abe ¹¹⁷ /2005	DB, PRCT 3 arms	RA on baseline MTX (7.2 ± 2 mg/wk)	3 mg/kg, 10 mg/kg or placebo	147	20-75	14 wk randomized 36 wk OLT	36 wk	Monthly hemograms	AEs NS between groups	5	Two deaths in 10 mg/kg group; TB monitoring by radiographs every 3 mo if first radiograph abnormal

(Continued)

Table 8—Continued

Author/Year	Study Design	Disease	Dose ^a	Route	No. Patients Treated	Age, y	Duration of Therapy	Duration of Monitoring	Complications Noted	Study Adequacy	Comments Malignancy/Death Pregnancy
Braun et al ²⁶ /2006	DB, PRCT 2:1 randomization to infliximab	Ankylosing spondylitis	5 mg/kg or placebo	266	32-47	6 mo	6 mo	NR	NR	4	AEs NR
van der Heijde et al ¹⁰ /2006	DB, PRCT 2:1 randomization to infliximab	Ankylosing spondylitis	5 mg/kg or placebo	279	32-47	6 mo	6 mo	NR	NR	2	AEs NR
Allaart et al ²⁵ /2006	DP, PRCT 4-armed trial of different initiation sequences of medications	RA	MTX 25-30 mg/wk + 3 mg/kg for 3 wk then increased to 6 mg/kg if ineffective	508	NR	12 mo	15 mo	AEs NS between groups	AEs NS between groups	4	Infliximab used with MTX in group 4
Seriolo et al ³⁴ /2007	OLT	RA on MTX and prednisone	3 mg/kg for three doses then every 8 wk	34	46-72	24 wk	24 wk	Total cholesterol and HDL cholesterol increased from controls ($P < .05$)	Total cholesterol and HDL cholesterol increased from controls ($P < .05$)	4	All women; data collected for all subjects on TNF blockade, including ETAN (n = 16), infliximab (n = 14), and adalimumab
Dahlqvist et al ¹³⁵ /2006	OLT, control cohort without infliximab	RA	3 mg/kg for three doses then every 8 wk	52	NR	24 mo	24 mo	Total cholesterol, LDL cholesterol, and HDL cholesterol elevated at 3 mo, 24-mo data still significant for total cholesterol	Total cholesterol, LDL cholesterol, and HDL cholesterol elevated at 3 mo, 24-mo data still significant for total cholesterol	3	Forty-two subjects treated with MTX ± prednisone

ACT = Active Ulcerative Colitis Trial; AE = adverse event; ANA = antinuclear antibody; Be ST = Behandel-Strategieën; HDL = high-density lipoprotein; LDL = low-density lipoprotein; RCT = randomized controlled trial; SAE = serious adverse event; TNF = tumor necrosis factor. See Table 5-7 legends for expansion of other abbreviations.

^aDose administered at 0, 2, and 64 wk and every 4 wk thereafter, unless otherwise noted.

thrombocytopenia, and pancytopenia. Similarly, severe hepatic reactions have been reported. Use of infliximab has been associated with reactivation of HBV infection. Infliximab therapy may lead to increases in total cholesterol and high-density lipoprotein levels.¹⁴³⁻¹⁴⁶ Others have suggested that atherogenicity may increase with intermediate-term therapy,¹⁴⁷ although this has not been consistent,¹⁴⁴ and the impact on cardiovascular disease is not clear. Cough was found more frequently in one COPD study with infliximab.⁹¹

3.1.3.2 Pregnancy Classification—Teratogenic effects have not been reported, but clinical experience is insufficient to establish the safety of infliximab during pregnancy.¹⁴⁸ It has been designated category B by the FDA.¹⁴⁸

3.1.3.3 Monitoring—Given the risk of TB and the high likelihood that this is related to reactivation of latent disease, recommendations for screening have been formalized.^{137,138} Observational studies have suggested that implementation of such a guideline has reduced TB reactivation by 80%¹⁴⁹; cases where guidelines were not followed showed a sevenfold higher incidence of TB.¹⁵⁰

Considerations for clinicians regarding infliximab for patients with lung disease and lung transplant recipients:

- *Assessing risk for TB:* Tuberculin skin testing and a chest radiograph should be obtained and reviewed prior to therapy. In addition, one should consider the risk for histoplasmosis, blastomycosis, or coccidiomycosis for patients living in or visiting endemic areas.
- *Assessing risk for hepatitis:* Hepatitis serology should be obtained prior to onset of therapy. Use of infliximab should be avoided if active viral hepatitis is present.
- *Monitoring blood work:* Patients with a history of viral hepatitis or chronic carrier states should be monitored for viral hepatitis reactivation as long as patients are receiving therapy.
- *Monitoring of drug clearance:* This is not applicable.
- *Monitoring for drug/drug interaction:* Live vaccines should be avoided while patients are being treated with infliximab.
- *Prophylaxis against infections:* No specific recommendations are available.

The following topics have been identified for prioritization for future research regarding infliximab:

- *The need for infection prophylaxis.*
- *The risk for reactivation of latent infection (eg, TB, histoplasmosis).*

- *The risk of malignancy.*
- *The appropriate strategy for monitoring for infection.*
- *The risk of heart disease exacerbation in patients with CHF.*

Information for patients:

- *Check your temperature frequently and report a fever to your physician immediately.*
- *Report to your physician signs of infection, such as cough, aches, fever, and chills; a wound or cut with redness, pain, discharge, or pus; pain; burning with urination; and nausea, vomiting, and diarrhea.*
- *Report shortness of breath or other changes in your breathing to your physician.*

Recommendations for the monitoring of anti-TNF- α agents in patients with lung disease and lung transplant recipients:

3.1a. For patients who will undergo anti-TNF- α therapy, a chest radiograph is recommended prior to treatment (Grade 1C).

3.1b. For patients who will undergo anti-TNF- α therapy, a tuberculin skin test is recommended to screen for latent TB prior to treatment (Grade 1C).

3.1c. For patients who will undergo anti-TNF- α therapy and present with a chest x-ray consistent with prior TB or a positive tuberculin skin test and/or are high-risk individuals, active TB infection should be excluded prior to treatment with adalimumab (Grade 1C), etanercept (Grade 1B), or infliximab (Grade 1B).

3.1d. For patients with latent *M tuberculosis*, active prophylactic treatment following published guidelines before initiation of anti-TNF- α therapy is recommended (Grade 1B).

3.1e. For patients with latent *M tuberculosis* who will undergo anti-TNF- α therapy, close monitoring for TB is recommended for up to 6 months after discontinuing therapy (Grade 1C).

3.1f. For patients who develop symptoms indicative of TB, prompt evaluation for active disease is recommended (Grade 1C).

3.1g. For patients with known grade III or IV New York Heart Association class heart failure, administration of adalimumab (Grade 1C), etanercept (Grade 1C), and infliximab (Grade 1B) is not recommended.

3.1h. For patients with a history of congestive heart failure who undergo anti-TNF- α therapy, close observation for congestive heart failure exacerbation is recommended (Grade 1C).

3.1i. For patients with a history of demyelinating disease, administration of etanercept is not recommended (Grade 1C), and administration of adalimumab and infliximab is not suggested (Grade 2C).

3.1j. For patients with no history of demyelinating disease who undergo anti-TNF- α therapy and experience symptoms or display signs of a demyelinating process, discontinuation of therapy is suggested (Grade 2C).

3.1k. For patients who undergo anti-TNF- α therapy and develop symptoms of a lupus-like disorder, discontinuation of therapy is suggested (Grade 2C).

3.1l. For patients who will undergo anti-TNF- α therapy and who are at risk for viral hepatitis, serologic screening for hepatitis B is recommended prior to treatment (Grade 1C).

3.1m. For patients who have hepatitis B virus infection, anti-TNF- α therapy should not be administered (Grade 1C).

3.1n. For patients who undergo anti-TNF- α therapy and develop unresolved infections, discontinuation of treatment until the infection is resolved is recommended (Grade 1B).

3.1o. For patients who are pregnant, administration of anti-TNF- α therapy is used only if alternatives are not able to be used (Grade 2C).

3.2 Calcineurin Inhibitors

3.2.1 Cyclosporin A: Although cyclosporin A (CsA) has regulatory approval for use in renal, liver, and cardiac transplantation, it has also been used in lung transplant recipients and in autoimmune diseases, including psoriatic arthritis and juvenile idiopathic arthritis. Two prospective, randomized trials compared cyclosporine with tacrolimus in patients following lung transplantation.^{151,152} There have been smaller studies evaluating CsA in living donor lung transplantation,¹⁵³ sarcoidosis,¹⁵⁴ and IPF¹⁵⁵ without significant benefit. Recently, aerosolization of CsA has been developed for use in lung transplantation. Open-label use of inhaled CsA (300 mg in 4.8 μ L propylene glycol) improved histologic rejection and lung function in a small group of patients ($n = 9$) with refractory acute rejection. Side effects included cough

and pharyngeal soreness.¹⁵⁶ The same group studied the addition of either inhaled CsA or placebo to a typical maintenance regimen after lung transplantation.^{157,158} Table 9 summarizes 11 studies reporting on adverse events associated with the use of CsA.^{151,152,154,159-166} Table 10 summarizes 15 studies reporting the use of CsA in various lung conditions.^{151-156,160,162-165,167-170}

3.2.1.1 Toxicity—One of the most common adverse events associated with CsA is nephrotoxicity.^{160,164, 172} CsA may also cause neurotoxicity, which can range from mild tremor or paresthesias to frank delirium and seizures. In addition, CsA may cause gingival hypertrophy,^{161,166} hypertension, hyperglycemia, hyperlipidemia, hirsutism, and the hemolytic-uremic syndrome. CsA in combination with other immunosuppressive agents after transplantation has been associated with an increase in bacterial, fungal, and viral infections. There is a higher risk of skin malignancies and lymphoproliferative disorders with the use of CsA.

3.2.1.2 Interactions With Other Drugs—CsA is metabolized through the hepatic cytochrome P450 system (CYP3A4)^{173,174}; therefore, any alteration of the P450 system either by medications or hepatic dysfunction will result in variable CsA trough levels.^{173,174} Additionally, several medications may interact with the P450 system and result in variability in CsA levels (Table 11).^{173,174} CsA may increase the concentration of bosentan when used together.^{173,174}

3.2.1.3 Pregnancy Classification—CsA has been categorized as category C by the FDA.¹⁷⁵ CsA crosses the placenta but has not been shown to be teratogenic in rats or rabbits,¹⁷⁵ and a case series of pregnant liver transplant recipients did not demonstrate an increased risk of maternal complications, congenital malformation, or impaired child development.^{176,177} However, the manufacturer does not recommend CsA use in pregnant women unless maternal benefit justifies potential risk to the fetus.¹⁷⁵ CsA may enter breast milk and cause potential immune suppression of the nursing infant.¹⁷⁵

3.2.1.4 Monitoring—When CsA is administered to transplant recipients, it is typically monitored daily until a steady level is attained that is in the target range. Levels can subsequently be obtained every 2 to 3 days until hospital discharge, with intervals gradually increased to every 1 to 2 weeks in the first 1 to 2 months posttransplant. Once stable levels are attained, subsequent levels can be monitored every 1 to 2 months. Levels must be monitored closely whenever medications that inhibit or accelerate CYP3A4-mediated clearance of CsA are added to or withdrawn from a patient's medication regimen. Additionally, the CBC count, potassium level, and renal function should be monitored at least every 4 to 6 weeks to monitor potential adverse effects of

Table 9—Monitoring of CsA (Adverse Events)

Author/Year	Nephrotoxicity	HTN	Infections	Gingival Hypertrophy	Hypercholesterolemia
Keenan et al ¹⁵¹ /1995	Similar to tacrolimus	Similar to tacrolimus	Pneumonia greater in CsA vs tacrolimus ($P = .0375$), fungal greater in tacrolimus vs CsA ($P < .05$).	More than tacrolimus	None or NR
Devineni et al ¹⁵⁰ /1984	12 of 14 patients (86%)	8 of 14 patients (57%)	0 infections	None or NR	None or NR
Zuckermann et al ¹⁵² /2003	10% at 12 mo Similar to tacrolimus	60% at 12 mo; similar to tacrolimus	CsA higher rate ($P = .059$); bacterial CsA ($P = .059$); fungal and viral same both groups	None or NR	75% at 12 mo; similar to tacrolimus
Wyser et al ¹⁵⁴ /1997	Increased significantly at 3, 9, and 18 mo	6 of 19 patients (32%)	11 of 16 patients (69%) developed bacterial infection	Present but less common	Increased but not different from prednisone alone
Trull et al ¹⁶⁵ /1999	Renal insufficiency with both Neoral and Sandimmune (both Novartis Pharmaceutical Corporation)	None or NR	1.82 infection/patient-y (Sandimmune) 1.71 infection/patient-y (Neoral)	None or NR	None or NR
Mikhail et al ¹⁶² /1997	Nonsignificant increase in serum Cr level with Neoral compared with Sandimmune	None or NR	None or NR	None or NR	None or NR
Glanville et al ¹⁶⁵ /2004	Improved serum Cr level with C2 monitoring	None or NR	None or NR	None or NR	None or NR
Griffiths et al ¹⁶⁰ /1996	All 22 patients developed histopathologic renal features	None or NR	None or NR	None or NR	None or NR
Tsimaratos et al ¹⁶⁴ /2000	GFR dropped in the first 6 mo then stabilized	66% developed HTN	At least one bacterial infection in all patients; viral infections were less common	None or NR	None or NR
Thomason et al ¹⁶⁶ /2005	None or NR	None or NR	None or NR	Multivariate modeling showed CsA dose correlated with gingival overgrowth	None or NR
Kilpatrick et al ¹⁶¹ /1997	None or NR	None or NR	None or NR	30 of 31 patients developed gingival overgrowth, which was most severe in younger patients	None or NR

Cr = creatinine; CsA = cyclosporin A; GFR = glomerular filtration rate; HTN = hypertension. See Table 6 and 7 legends for expansion of other abbreviations.

Table 10—Monitoring of CsA for Lung Disease

Author/Year	Disease	Dose	No. Patients Treated	Study Design	Complications Noted
Keenan et al ¹⁵¹ /1995	Lung transplant	2.5 mg/kg/d 4	133	RCT	Prospective: Acute rejection: lower in tacrolimus vs CsA ($P = .NS$); BO: greater in CsA vs tacrolimus ($P = .025$). Infections: pneumonia greater in CsA vs tacrolimus ($P = .0375$), and fungal greater in tacrolimus vs CsA ($P < .05$). Renal dysfunction: equal both groups
Trull et al ¹⁶⁵ /1999	Lung transplant	q12h non-CF; q8h CF to achieve target trough blood concentration (range, 200–300 µg/L)	50; 289 of 343 profiles analyzed	RCT, SB	Prospective: C ₂ ($P < .001$) and AUC _{0–6} ($P < .002$) lower in Neoral vs Sandimmune (both Novartis Pharmaceutical Corporation); CrCl decreased from baseline, NS between groups; mean reciprocal serum Cr level increased in both groups ($P < .001$). Infectious rates: no difference
Zuckermann et al ¹⁵² /2003	Lung transplant	1 mg/kg/d IV, then po	74	RCT, OL, 2 center	Prospective: Acute/recurrent rejection: no difference between groups. BO: three in each group. Infection: CsA higher rate ($P = .059$); bacterial CsA ($P = .089$); fungal and viral same both groups. AEs: Cr levels were the same in both groups; renal dysfunction increased to 12 mo; HTN: CsA greater ($P = .03$). New-onset diabetes: only in tacrolimus group. Leukopenia: similar in both groups. GI effects: similar. Malignancies: two in CsA group.
Venuta et al ¹⁵⁵ /1993	IPF prior to lung transplant	4–7 mg/kg/d po	10	Clinical trial	With introduction to CsA, seven of 10 were weaned from prednisone, three had transplants, two were on waiting list, two died, and three were nonresponders; four of seven had infectious complications.
Shennib and Auger ¹⁷¹ /1994	CF lung transplant	8.1 ± 2.6 mg/kg with diltiazem po	8	Cohort	NR
Griffiths et al ¹⁶⁰ /1996	Heart and lung transplant	450–550 ng/mL for 1 mo; 300–400 ng/mL po for 3 mo	22	Cohort	Seven patients had renal failure; 16 had proteinuria levels of > 3 g/d; six died; three were receiving dialysis; three received renal transplants; and nine had renal impairment
Iacono et al ¹⁵⁶ /1997	Acute lung rejection	300 mg at flow rate of 10 L/min/d aerosolized	9	Cohort	NR of hepatotoxicity or nephrotoxicity; AEs: cough, pharyngeal soreness, breathlessness; FEV ₁ = NS
Wyser et al ¹⁵⁴ /1997	Sarcoidosis	5–7 mg/kg/d po	37 (7 enrolled 2 times)	OL RCT	No benefit when added to prednisone for sarcoidosis. Infection: bronchitis, pneumonia, sinusitis; Cr level: significant increase ($P < .05$); paresthesias: 11 patients; HTN: four patients
Mikhail et al ¹⁶² /1997	CF	417–471 ng/mL dose tapered over 18 mo Neoral po	36	Cohort	No AEs reported; Neoral causes significant increase in AUC and C _{max}

(Continued)

Table 10—Continued

Author/Year	Disease	Dose	No. Patients Treated	Study Design	Complications Noted
Tsimaratos et al ¹⁶⁴ /2000	Pulmonary transplant pediatric patients	Maximum of 400 mg/mL IV 5-15 d then po	19	Cohort	Acute rejection: 1.5 per patient in year 1 (most within first 6 mo) Infection: bacterial infections in every patient × 1; viral infections frequent
Knoop et al ¹⁶⁵ /2003	CF/non-CF lung transplant	Mean dose, 250 mg q12h CF; 170 mg q12h non-CF	20	OL	Kidney function: decreased in all patients; PCr increased; GFR increased AUC per dose smaller significantly in CF than non-CF. Patients with CF show lower bioavailability of CsA
Glanville et al ¹⁶⁶ /2004	Heart/heart-lung transplant	6.4 ± 7.3 mg/kg/d reduced to 3.9 ± 3.7 mg/kg/d; target C ₀ levels 400 µg/L; C ₂ target levels 300-600 µg/L	15	Cohort	With conversion from C ₀ to C ₂ monitoring CsA could be reduced and renal dysfunction improved
Date ¹⁵³ /2004	Lung transplant (LDLLT)	100 mg/d adjusted to maintain trough levels (NG tube)	16	Cohort	Decreased urine output; acute rejection in four patients Infection: NR
Morton et al ¹⁶⁹ /2004	Lung transplant	8-10 mg/kg/d po	36	Two 18-person group cohort comparison	C ₀ group: significant increase in serum Cr level vs baseline Vascular rejection: NS between C ₀ and C ₂ groups Bronchial rejection: NS between groups Infection rate: NS between groups C ₂ monitoring demonstrated a significant reduction in rise of serum Cr level posttransplant
Jaksch et al ¹⁷⁰ /2005	Lung transplant	Mean dose, 330 mg/d (range, 150-950 mg/d)	20	Cohort	C ₂ time point showed highest correlation; C ₀ time point had poorest correlation with AUC ₀₋₄

AUC = area under the curve; BO = bronchiolitis obliterans; CF = cystic fibrosis; Cmax = maximum plasma concentration; CrCl = living donor lobar lung transplantation; NG = nasogastric; PCr = plasma creatinine; SB = single-blind. See Tables 5-9 legends for expansion of other abbreviations.

Table 11—Summary of Drug/Drug Interactions

Drug Class	Specific Drug	Metabolized by CYP 3A4	Imidazole Antifungal Agents	Macrolides	Other Antibacterial Agents	Corticosteroids	Antiarrhythmics	Anticonvulsants	Vaccines	Anakinra	NSAIDs	ACE Inhibitors	Thiazide Diuretics	Proton Pump Inhibitors	Allopurinol	Warfarin	Statins	Antacids	Grapefruit juice	Echinacea	Herbal Teas, Diet Supplements
Anti-TNF agents	Adalimumab								+	+										+	+
	Etanercept								+	+										+	+
CNIs	Indinavir																			+	+
	CsA	+	++	++	++	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cytolytic antibodies	Tacrolimus	+	++	++	++	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
	Abatacept								+	+											
ATG	Muromonab								+												
	Anti-CD3								+												
IL-2 antagonists	Basiliximab								+											+	+
	Simeprevir								+											+	+
Cytotoxic agents	AZA								+			+								+	+
	CYC								+											+	+
Leflunomide	MTX								+												
	MPA								+												
mTOR inhibitors	Everolimus	+																			
	Sitagliptin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Other agents	CQ/HCC								+												
	Infliximab	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

See text of individual agents for details. Antiarrhythmic drugs may have different interactions based on class of antiarrhythmic. CYP3A4-metabolized agents (competitors, increased levels of other drugs metabolized by CYP3A4) include the following: nefazodone, macrolides, imidazoles, cimetidine, chloramphenicol, grapefruit juice, calcium channel blockers, and dalfopristin/quinnipristin. CYP3A4 inducers (decreased drug level due to increased activity of CYP3A4) are as follows: phenytoin, phenobarbital, primidone, modafinil, carbamazepine, rifampin. Other antibacterial agents are as follows: quinolones (with QT and metabolism issues) and β -lactams. Anticonvulsants may be inducers (phenobarbital, carbamazepine, phenytoin) or inhibitors (valproic acid). ACE = angiotensin-converting enzyme; ATG = antithymocyte globulin; AZA = azathioprine; CNI = calcineurin inhibitor; CQ = chloroquine; CYP3A4 = cytochrome P450 system; HCC = hydroxychloroquine; MPA = mycophenolic acid; mTOR = mammalian target of rapamycin. See Table 5, 6, 8, and 9 legends for expansion of other abbreviations.

CsA on these parameters. More frequent monitoring should be done when patients are admitted to the hospital with posttransplant complications.

In general, clinicians have followed the trough level of CsA (C_0) and adjusted dosage accordingly. Recently, there has been concern that this measurement does not correlate well with area-under-the-curve exposure to CsA.¹⁶⁸ As a result, more centers are considering monitoring CsA concentration by the level of CsA 2 h after the dose is administered (C2 monitoring). In addition, de novo C_2 monitoring may be associated with improved renal function in patients receiving CsA.^{165,169,170} In general, target trough CsA levels are between 250 and 400 ng/mL, and C2 levels are targeted between 600 and 1,500 ng/mL.

Considerations for clinicians regarding CsA for patients with lung disease and lung transplant recipients:

- *Monitoring blood work:* In addition to monitoring cyclosporine levels regularly, CBC count, renal function, glucose level, lipid profile, and potassium and magnesium levels should be monitored closely. BP should be measured frequently after initiating cyclosporine.
- *Monitoring of drug clearance:* CsA is metabolized through the hepatic mixed-function oxidase system (CYP3A4) and excreted through the liver, although both the kidney and the gut may contribute to its elimination. Various medications are known to either increase or decrease cyclosporine concentrations by either inhibiting or inducing the CYP3A4 system. See the following section for details.
- *Monitoring for drug/drug interaction:* CsA is metabolized through the CYP3A4 system. As a result, drugs that affect this system will affect clearance of cyclosporine. In addition, CsA is

an inhibitor of the CYP3A4 and may reduce the clearance of several medications, including digoxin, colchicine, and the β -hydroxy- β -methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors. Table 11 summarizes some of the important drug/drug interactions.

- *Prophylaxis against infections:* Prophylaxis against *P. jiroveci* should be implemented with the use of CsA. Prophylaxis recommendations are discussed in Table 12.

The following topics have been identified for prioritization for future research regarding CsA:

- *The benefit of cyclosporine trough monitoring compared with monitoring levels 2 h after administration of CsA.*
- *The frequency of monitoring blood work and cyclosporine levels.*

Information for patients:

- *Adverse events associated with CsA are acne, dizziness, headache, increased hair growth, nausea and vomiting, diarrhea, stomach discomfort, numbness, tingling, stomach bleeding, high BP, kidney problems, liver dysfunction, and hypercholesterolemia.*

3.2.2 Tacrolimus: Tacrolimus is FDA approved for the prophylaxis of organ rejection in patients receiving allogeneic liver, kidney, or heart transplants and for treatment of severe atopic dermatitis. In addition to FDA-approved indications, tacrolimus has been used for antirejection prophylaxis in pancreatic, intestinal, and lung transplantation.¹⁷⁸ It has also been used to treat graft-vs-host disease, rheumatologic disorders (lupus erythematosus, rheumatoid arthritis, scleroderma, polymyositis), inflammatory

Table 12—Infection Prophylaxis for Intense Immunosuppression

Infectious Agent	Agents	Alternatives
<i>Candida</i> species	Clotrimazole (topical, troches) Ketoconazole (po, IV) ^a	Other imidazole
<i>Aspergillus fumigatus</i>	Inhaled nebulized amphotericin B Imidazoles (itraconazole, voriconazole)	Caspofungin
<i>Pneumocystis jiroveci</i>	Trimethoprim/sulfamethoxazole	Inhaled pentamidine (monthly) Dapsone Atovaquone
Herpesviruses	Acyclovir Valacyclovir	
CMV	Ganciclovir Valganciclovir	Used only for ganciclovir-resistant CMV (maribavir, leflunomide, sirolimus-ganciclovir, artesunate, high-dose ganciclovir)

CMV = cytomegalovirus.

^aNot needed if other imidazoles active against *A. fumigatus* are being given.

Table 13—Monitoring of Tacrolimus for Lung Disease

Author/Year	Study Design	Disease	Dose ^a	No. Patients Treated	Age, y	Duration of Therapy	Duration of Monitoring	Monitoring Used	Complications Noted	Study Adequacy	Comments Malignancy/Death Pregnancy
Kesten et al ¹⁵⁹ /1997	Open, nonrandomized study in patients with new diagnosis of BOS nonresponsive to usual therapy, switch from CsA to tacrolimus	Lung transplant with BOS	NA	12	30-50	6 mo	6 mo	Tacrolimus target 10-20 through Abbott IMX test (Abbott Laboratories)	A mild drop in magnesium level, but still normal; hyperglycemia in one patient (6.6%), two (13%) with increase in insulin doses; seven patients (46%) with at least 20% increase in Cr level	1	Twelve of 15 patients had the results of the PFTs for 6 mo but unclear whether the three patients with no PFTs were still receiving therapy
Sarahrudi et al ¹⁵⁷ /2002	Open, nonrandomized study in patients with refractory acute rejection or BOS, switch from CsA to tacrolimus	Lung transplant with refractory acute rejection or BOS	NA	19	28-54	14 mo (4-24 mo)	Same as duration of therapy	Every 2 wks Mean level was 11.7 ± 2.9 ng/mL	The Cr level rose from 1.4 ± 0.4 to 1.8 ± 2.5 mg/dL	1	Three patients died of sepsis, pancreas carcinoma, and BOOP
Ross et al ¹⁵⁸ /1997	Open, nonrandomized study (CS) in patients with new diagnosis of BOS nonresponsive to usual therapy, switch from CsA to tacrolimus	Lung transplant with BOS	0.025-0.05 mg/kg/d in two divided doses	10	NA	3-24 mo; mean, 15	Same as duration of therapy	Tacrolimus target 10-15 ng/mL through IMX in Cr < 2 mg/dL level, if Cr > 2 mg/dL level 7-10 ng/mL	Increased Cr > 2 in three patients (30%)	1	Two recipients with hypercapnic respiratory failure died

(Continued)

Table 13—Continued

Author/Year	Study Design	Disease	Dose ^a	No. Patients Treated	Age, y	Duration of Therapy	Duration of Monitoring	Monitoring Used	Complications Noted	Study Adequacy	Comments Malignancy/Death Pregnancy
Onsager et al ¹⁸ /1999	Open, nonrandomized study in patients with heart or lung transplant with refractory rejection	Lung transplant with refractory rejection	1-6 mg	15 lung	31-58	17.1 mo	17.1 mo	Tacrolimus target, 10-20 ng/mL through IMX	Combined for heart (n = 15) and lung (n = 15) transplant patients; hyperglycemia (n = 13 [43%]), diarrhea (n = 12 [40%]), nephrotoxicity (n = 9 [30%]) reported for increase of baseline Cr level of 1-1.5 mg/dL, tremor (n = 5 [17%]), HTN (n = 1 [3%]), nausea (n = 1 [3%])	1	Four of 15 patients died following the development of BO
Mentzer et al ¹⁹ /1998	Six centers, Open, nonrandomized study in patients with heart or lung transplant with refractory rejection or who did not tolerate CsA	Heart or lung transplant with refractory rejection	0.075-0.15 mg/kg	15 lung, but only eight completed the study	Mean, 49.3; range, 21-66	169 ± 86 d; range, 42-311 d	<1 y	Tacrolimus target, 10-40 ng/mL through IMX Results: 1-3 mo, 16 ng/mL; >3 mo, 9 ng/mL	Cr level increased in lung transplant recipients 1.42-1.6 mg/dL, increased Cr level, 26%; diarrhea, 13.3%; headache, 13.3%; pneumonia, 20%; nausea, 20%; depression, 6.7%; fever, 6.7%; tremor, 6.7%; vomiting, 6.7%	1	Five patients died, one retransplant was removed by physician preference

(Continued)

Table 13—Continued

Author/Year	Study Design	Disease	Dose ^a	No. Patients Treated	Age, y	Duration of Therapy	Duration of Monitoring	Monitoring Used	Complications Noted	Study Adequacy	Comments Malignancy/Death Pregnancy
Griffith et al ¹⁷⁹ /1994	Randomized, unblinded clinical trial of CsA vs tacrolimus as initial therapy posttransplant, no description of randomization method (alternative)	Immediately post-lung transplant	0.025-0.075 mg/kg/d Four infusions, then orally 0.15 mg/kg/d divided bid	38	21-66	At least 6 mo	At least 6 mo	ELISA but no levels reported for CsA or tacrolimus	Twelve patients (31%) had HTN, similar to CsA; described less hirsutism and gingival dysplasia, but no numbers	2	Study descriptive with few numbers or any intentions to describe complications or side effects
Keenan et al ¹⁵¹ /1995	Randomized, unblinded clinical trial of CsA vs tacrolimus as initial therapy posttransplant, no description of randomization method (alternative)	Immediately post-lung transplant	0.025-0.075 mg/kg/d Four infusions, then orally 0.15 mg/kg/d divided bid	66	20-66	257-1,049 d 8.5-34 mo	2 y	ELISA but no levels reported for CsA or tacrolimus, then changed to the IMX levels 10-20 ng/dL	Incidence of fungal infections higher 0.49 ± 1.77 vs 0.1 ± 0.28 with CsA; at 1 y posttransplant, mean Cr level 1.95 ± 0.72 vs 1.68 ± 0.6 mg/mL in the CsA group; described less hirsutism and gingival dysplasia but no numbers	2	...

(Continued)

Table 13—Continued

Author/Year	Study Design	Disease	Dose ^a	No. Patients Treated	Age, y	Duration of Therapy	Duration of Monitoring	Monitoring Used	Complications Noted	Study Adequacy	Comments Malignancy/Death Pregnancy
Zuckermann et al ¹³² /2003	Randomized with some controlling and unblinded de novo therapy posttransplant	Immediately post-lung transplant	0.015 mg/kg/d 37 Four infusions, then orally 0.1–0.3 mg/kg/d divided bid	37	24–65	365–910 d 12–30 mo	Levels	First month, 12–15 ng/dL, then 9–12 ng/dL	No statistically significant difference in infections; renal dysfunction Cr > 2 at 6 mo was 5% and 16% at 12 mo de novo diabetes, 11% vs 0% in the CsA group; less HTN than the CsA group (60% vs 11%, <i>P</i> = .03); leukopenia in 22%, no difference with CsA	2	...
Treede et al ¹³⁶ /2001	Randomized with some controlling and unblinded de novo therapy posttransplant	Lung transplant	0.05 mg/kg/d immediately after surgery, and then switched to oral tacrolimus 0.1–0.3 mg/kg/d after extubation	Tacrolimus, 26 CsA, 24	NA	Median, 525 d	1 y	Acute rejection Patient survival Infection episodes Side effects	Four patients switched from CsA to tacrolimus; two CsA patients had to be retransplanted	1	...

(Continued)

Table 13—Continued

Author/Year	Study Design	Disease	Dose ^a	No. Patients Treated	Age, y	Duration of Therapy	Duration of Monitoring		Monitoring Used	Complications Noted	Study Adequacy	Comments	
												Malignancy/Death	Pregnancy
Wiebe et al ¹⁵⁵ /1998	OL, uncontrolled study	Lung or heart-lung transplant with BOS or severe acute rejection	Adjusted to levels	34	NA	15 (range, 3-42 mo)	Level, 10-20 ng/dL		Diabetes in one patient (3%), rise in Cr level (no description of the change) in six patients (17%), tremor, pruritus, and depression in five patients (15%)	1	...	...	...
Barten et al ¹⁵⁹ /2005	Comparison of lymphocyte inhibition in patients changed from CsA to tacrolimus	Lung and heart transplants	6 mg bid	Two lung Six heart	NA	5 d	Levels measured by Emit (Siemens Healthcare Diagnostics Inc) First day, 3-13.6 ng/mL on day 5		No description of side effects	1	...	...	...
Knoop et al ¹⁵⁹ /2005	Prospective pilot study (only 5 d to have a PK study) of 22 patients with or without CF already on tacrolimus posttransplant (mean posttransplant over 30 mo)	Lung transplant CF	Median dose, 6 mg bid in CF and 3 mg bid on non-CF	11 CF 11 non-CF	CF median, 30 (range, 21-43) Non CF median, 51 (range, 31-56)	At least 3 mo of tacrolimus before the study but only follow-up for 1 wk for the PK studies	5 d		No description of side effects	1	...	...	...
Faivre et al ¹⁵² /2001	Prospective nonrandomized study following the doses of tacrolimus used in transplantation	Transplant patients: Liver, 191 Kidney, 94 Heart, 10 Lung, 8 Multiple transplant, 14	Initiation, 4.4 mg/d 6 mo, 7.43 mg/d 1 y, 6 mg/d	8, but only 4 in the initial period	Lung, 15.6 ± 7.4	4 y in lungs up to 7.5 y in livers	4 y in lungs up to 7.5 y in livers		No description	1	...	...	...

(Continued)

Table 13—Continued

Author/Year	Study Design	Disease	Dose ^a	No. Patients Treated	Age, y	Duration of Therapy	Duration of Monitoring	Monitoring Used	Complications Noted	Study Adequacy	Comments Malignancy/Death Pregnancy
Sarahrudi et al ¹⁸⁹ /2004	Retrospective MC study to evaluate conversion from CsA to tacrolimus	13 European, Australian, and Canadian centers 244 patients with persistent AR or BOS	NA	244	38 ± 114	16-18 mo	NA	NA	Cr level increased from 1.3-1.5 mg/mL in persistent rejection and from 1.5-1.7 mg/mL in BOS; no changes in infections; no description of other side effects	1	...
Reichenspumer et al ¹⁸⁵ /1999	Retrospective description of three immunosuppression regimens in 86 patients	CsA, AZA, and ATG, n = 34 Tacrolimus, AZA, ATG, n = 30 Tacrolimus, MMF, 12	IV 0.5 mg/kg/d after surgery, then 0.1-0.3 kg/d	42	Mean, 40 ± 15 (range, 16-61)	14 ± 5.6 mo	Not described	NA	Cr > 2; tacrolimus vs CsA, 13.3% vs 17.6%; hyperglycemia not defined; tacrolimus vs CsA, 26% vs 14%, 10% insulin requirements (three patients in each group)	1	...
Heisel et al ¹⁸⁸ /2004	Systematic review and meta-analysis of new-onset diabetes with CNIs	One retrospective lung study (Reichenspumer et al ¹⁸⁴)	Multiple studies, not described in the article	See Reichenspumer et al ¹⁸⁵ article	See Reichenspumer et al ¹⁸⁵ article				Incidence of IDDM, 10.4% among tacrolimus-treated patients	1	...

AR = allograft rejection; BOOP = bronchiolitis obliterans organizing pneumonia; BOS = bronchiolitis obliterans syndrome; ELISA = enzyme-linked immunosorbent assay; IDDM = insulin-dependent diabetes mellitus; MMF = mycophenolate mofetil; PK = pharmacokinetics. See Table 5, 7, and 9-11 legends for expansion of other abbreviations.

bowel disease, various skin conditions other than atopic dermatitis, and uveitis. Table 13 summarizes the 16 clinical trials reporting on the use of tacrolimus for various lung diseases.^{151,152,179-192}

3.2.2.1 Toxicity—The FDA has issued a black box warning for increased susceptibility to infection and the possible development of lymphoma.¹⁹³ Tacrolimus and CsA have several common toxicities due to the similar nature of these agents.^{193,194} In addition to infection and possible increased risk of malignancy, tacrolimus administration has been associated with nephrotoxicity, systemic hypertension, dyslipidemia, bone marrow suppression, hyperkalemia, hyperglycemia, hypomagnesemia, diabetes mellitus, cardiac toxicity, and neurotoxicity.¹⁹³

3.2.2.2 Interactions With Other Drugs—Tacrolimus is metabolized through the hepatic mixed-function oxidase system (CYP3A4).^{174,193,195,196} Perturbation of the P450 system by medications or hepatic dysfunction will alter (increase) tacrolimus trough levels.^{174,193,195,196} Additionally, several medications, especially imidazoles, may interact with the P450 system and result in variability in tacrolimus levels.^{174,193,195,196} High-fat meals may decrease the oral absorption area under the curve by 37%, with a 77% decrease in maximum plasma concentration. St John's wort may also decrease tacrolimus levels.

3.2.2.3 Pregnancy Classification—Tacrolimus has been designated class C for pregnancy risk by the FDA for all trimesters.¹⁹³ Although it crosses the placenta, no causal relationship between teratogenic effects and tacrolimus administration has been identified in humans.^{193,197} However, the manufacturer does not recommend tacrolimus use in pregnant women unless maternal benefit justifies potential risk to the fetus. Tacrolimus may enter breast milk and cause potential immune suppression of the nursing infant.¹⁹³

3.2.2.4 Monitoring—Tacrolimus levels can be obtained through an enzyme immunoassay using monoclonal antibodies,¹⁹⁸ and other techniques are available. The recommended trough levels after lung transplantation range between 5 and 15 ng/mL. When tacrolimus is administered to transplant recipients, it is typically monitored daily until a steady level is attained that is in the target range. Levels can subsequently be obtained every 2 to 3 days until hospital discharge, with intervals gradually increased to every 1 to 2 weeks in the first 1 to 2 months posttransplant. Once stable levels are attained, subsequent levels can be monitored every 1 to 2 months. Levels must be monitored closely whenever medications that inhibit or accelerate CYP3A4-mediated clearance of tacrolimus are added to or withdrawn from a patient's medication regimen. Additionally, the CBC count should be monitored intermittently to detect significant bone

marrow suppression, and intermittent measurement of serum potassium and glucose levels, renal function, and hepatic function may detect tacrolimus-induced abnormalities in these parameters.^{174,193} Such monitoring should be done at least every 4 to 6 weeks to monitor potential adverse effects of tacrolimus on these parameters. More frequent monitoring should be done when patients are admitted to the hospital with posttransplant complications.

Considerations for clinicians regarding tacrolimus for patients with lung disease and lung transplant recipients:

- *Monitoring blood work:* In addition to monitoring tacrolimus levels regularly, CBC count, renal function, glucose level, lipid profile, and potassium and magnesium levels should be monitored closely. BP should be measured frequently after initiating tacrolimus.
- *Monitoring of drug clearance:* Tacrolimus is metabolized through the hepatic mixed-function oxidase system (CYP3A4) and excreted through the liver, although both the kidney and the gut may contribute to its elimination. Various medications are known to either increase or decrease tacrolimus concentrations by either inhibiting or inducing the CYP3A4 system.
- *Monitoring for drug/drug interaction:* Because tacrolimus is metabolized through the CYP3A4 system, drugs that affect this system will affect clearance of tacrolimus. In addition, tacrolimus is an inhibitor of CYP3A4 and may reduce the clearance of several medications, including digoxin, colchicine, and the HMG-CoA reductase inhibitors. Some of the drug/drug interactions are summarized in Table 11.
- *Prophylaxis against infections:* Prophylaxis against *Pneumocystis jiroveci* should be implemented with the use of tacrolimus. Prophylaxis recommendations are discussed in Table 12.

The following topics have been identified for prioritization for future research regarding tacrolimus:

- *The optimal approach to measuring blood levels of tacrolimus (trough monitoring compared with monitoring peak levels 2 h after administration of tacrolimus).*
- *The frequency of monitoring blood work and tacrolimus levels.*

Information for patients:

- *Adverse events associated with tacrolimus are acne, dizziness, headache, increased hair growth,*

nausea and vomiting, diarrhea, stomach discomfort, numbness, tingling, stomach bleeding, high BP, kidney problems, liver problems, and increased cholesterol levels.

Recommendations for the monitoring of calcineurin inhibitors (CNIs) in patients with lung disease and lung transplant recipients:

3.2a. For patients who will undergo CNI therapy, the monitoring of drug concentrations, BP, glucose, potassium, magnesium, lipids, CBC count, and renal function is recommended (Grade 1B).

3.2b. For patients who undergo CNI therapy, monitoring of drug levels when CYP3A4 inducers or inhibitors are added or stopped and adjusting doses are recommended when using cyclosporin A (Grade 1A) or tacrolimus (Grade 1B) therapy.

3.2c. For lung transplant recipients receiving CNI therapy who develop renal dysfunction, a reduction in the target dose concentration is suggested (Grade 2C).

3.3 Antilymphocyte Antibodies

3.3.1 Alemtuzumab: Alemtuzumab is administered intravenously and has regulatory approval for the second-line therapy of B-cell chronic lymphocytic

leukemia.¹⁹⁹⁻²⁰¹ Alemtuzumab has also been used to treat autoimmune cytopenias, non-Hodgkin's lymphoma, and T-cell prolymphocytic leukemia.¹⁹⁹⁻²⁰¹ Alemtuzumab is used as induction therapy prior to solid organ transplant, including lung transplant.¹⁹⁹⁻²⁰¹ Some experience has been reported for its use in treatment of acute solid organ rejection.¹⁹⁹⁻²⁰¹ A summary of common clinically significant side effects of alemtuzumab is presented in Table 14.²⁰²⁻²⁰⁴ A summary of other clinically significant side effects of alemtuzumab is presented in Table 15.^{205,206} Table 16 summarizes the one report on using alemtuzumab for lung disease.²⁰⁷

3.3.1.1 Toxicity—Administration reactions are common, particularly when alemtuzumab is used for hematologic malignancies. These infusion reactions, including hypotension, rigors, fever, shortness of breath, bronchospasm, chills, and rash, are managed by slow dose titration and premedication with diphenhydramine and acetaminophen.²⁰⁵ The cytokine release with alemtuzumab administration is managed in solid-organ transplant patients by pretreatment with high doses of methylprednisolone.

Other serious adverse effects following administration of alemtuzumab include autoimmune hematologic toxicities²⁰⁵ and autoimmune thyroid disease.²⁰⁶ Clinicians in a variety of transplant settings have been keenly aware of the possibility of infection with the profound and sustained lymphopenia induced by alemtuzumab. Infectious complications have been

Table 14—Common Clinically Significant Side Effects of Alemtuzumab

Author/Year	Fever		Type of Infection	Alemtuzumab, %	Placebo or Other Induction Agent, %
	Alemtuzumab, %	Placebo, %			
Vathsala et al ²⁰⁴ /2005 (kidney transplant)	35	0	Cytomegalovirus	45	20
			Herpes zoster	5	0
			Septicemia	10	0
			Pneumonia	25	0
			Urinary tract	45	60
			<i>Pneumocystis carinii</i> pneumonia	5	0
			Moderate to severe infection (total patients)	40	30
Knechtle et al ²⁰² /2004 (kidney transplant)			Not specified	~45 patients 1 y posttransplant	~55 patients 1 y posttransplant
Ciancio et al ²⁰³ /2005 (kidney transplant)			Pneumonia	3	0
			Bacteremia	3	7
			Sepsis	0	3
			Urinary tract	3	1.5
			Cytomegalovirus	0	1.5
			Lymphocele	3	0
			Osteomyelitis	0	1.5
			Abscess	1	5
			Cellulitis	3	1.5
			Moderate to severe infection (total patients)	20	18

Table 15—Other Drug-Specific Clinically Significant Side Effects of Alemtuzumab

Side Effect	Incidence/100,000	References	Monitoring Used	References
Hyperthyroid	Not stated	Kirk et al ²⁰⁶ /2006	Triiodothyronine, free thyroxine, thyroid-stimulating hormone	Kirk et al ²⁰⁶ /2006
PTLD in lung transplant patients	2/56	Campath (Genzyme Corp) package insert ²⁰⁵	NA	NA

PTLD = posttransplant lymphoproliferative disease. See Table 7 legend for expansion of other abbreviation.

similar to standard immunosuppression regimens in several reports.^{202-204,207,208} In one large series of transplant patients, more serious infections were reported in patients with lung, intestinal, or multivisceral transplants compared with other solid organ transplants and when alemtuzumab was used to treat rejection than if used for induction.²⁰⁹

3.3.1.2 Pregnancy Classification—Alemtuzumab is pregnancy category C.²⁰⁵ No reports of alemtuzumab use in pregnancy and lactation have been published. However, IgG crosses the placenta, and depletion of the fetal lymphocytes is possible. IgG also is present in human milk, but the alemtuzumab concentrations in milk and infant absorption of the drug have not been measured.²⁰⁵

3.3.1.3 Monitoring—The manufacturer recommends that CBC and platelet counts be obtained at weekly intervals during therapy and that patients be monitored for infusion reactions.²⁰⁵ Assessment of CD4⁺ lymphocyte counts following treatment to ascertain recovery to a $\geq 200/\mu\text{L}$ concentration has also been recommended.²⁰⁵

Considerations for clinicians regarding alemtuzumab for patients with lung disease and lung transplant recipients:

- *Monitoring the administration of the drug:* Monitoring for infusion reactions should be undertaken during drug infusion (eg, pulmonary edema, systemic inflammatory response syndrome [SIRS]).
- *Monitoring blood work:* CBC count and hepatic and renal function should be monitored periodically as patients are receiving therapy. Daily CBC count and hepatic and renal function laboratory results should be obtained during the initiation of therapy, and subsequent intervals of testing will depend on clinical response. If reinstitution of therapy is considered following prior exposure, laboratory evaluation for host antibodies (where available) before reinstitution of therapy should be considered.
- *Monitoring of drug clearance:* Doses may be adjusted following thrice-weekly assays to suppress sheep erythrocyte rosette levels of circulating

mononucleated cells to $<10\%$. Alternative dose adjustment monitoring approaches are aimed to maintain CD3 counts of $<20/\mu\text{L}$ and CD2 counts of $<50/\mu\text{L}$.

- *Monitoring for drug/drug interaction:* Alemtuzumab frequently is used in combination with other immunosuppressive agents. Therefore, additive or synergistic suppression of host immunity (particularly lymphocyte-based defenses) can occur when this agent is used with other immunosuppressive therapies.
- *Prophylaxis against infections:* Alemtuzumab increases risk for certain infections, such as atypical bacterial infections; fungal infections, including *Pneumocystis* pneumonia; and viral infections, including cytomegalovirus (CMV). Prophylaxis for *Pneumocystis* pneumonia should be considered in all patients. Careful monitoring for other infections should be implemented in all patients.

The following topics have been identified for prioritization for future research regarding alemtuzumab:

- *How frequently one needs to monitor CBC count and hepatic function.*
- *The appropriate medications useful for preventing or minimizing infusion reactions.*

3.3.2 Antithymocyte Globulin: Equine antithymocyte globulin (ATG) has received FDA approval for use in aplastic anemia, in the treatment of renal transplant rejection, and in prophylaxis of renal transplant rejection, whereas rabbit-derived ATG is approved for use in the treatment of renal transplant rejection.²¹⁰⁻²¹² ATG has been used in non-FDA-approved indications for lung transplant rejection and prophylaxis, where the evidence supports a favorable outcome in these clinical situations.²¹⁰⁻²¹² ATG is almost always used in combination with other immunosuppressive agents.²¹⁰⁻²¹² Table 17 summarizes one trial of ATG for renal transplant patients and provides detailed information regarding toxicity.²¹³

3.3.2.1 Toxicity—ATG (equine) is contraindicated in patients with a personal history of hypersensitivity

Table 16—Monitoring of Alemtuzumab

Author/Year	Study Design	Disease	Dose	No. Patients Treated	Age, y	Duration of Therapy	Duration of Monitoring	Monitoring Used	Complications Noted	Study Adequacy	Comments
McCurry et al ^{207/2005}	Retrospective review with historical controls	Lung transplant	Alemtuzumab 30 mg, thymoglobulin 4-7 mg/kg, daclizumab 1 mg/kg × 5 doses	Alemtuzumab, 10; thymoglobulin, 38; daclizumab, 28	22-70	Alemtuzumab and thymoglobulin one dose prior to transplant, daclizumab at 10 wk	6 mo	Spirometry 2 and 8 wk and every 2-3 mo; surveillance BAL and biopsy 2 and 8 wk and every 2-3 mo; lymphocyte counts by flow cytometry at 1, 7, 14, 30, 90, and 180 d	Lymphocyte depletion sustained for at least 6 mo; no increase in infections detected	NA	Alemtuzumab, 1 death; thymoglobulin, 1 death and 1 graft loss; daclizumab, 3 deaths

See Table 7 legend for expansion of abbreviation.

Table 17—Monitoring of Antithymocyte Globulin

Author/Year	Disease	Dose	Route	No. Patients Treated	Study Design	Complications Noted	Comments
Soulillou et al ^{213/1990}	Renal allografts	Antithymolimus, 10 mg/d; ATG dose not specified	IV	100 consecutive renal allograft patients	RCT	Graft rejection, infectious complication, allergic reaction	ATG resulted in greater reduction in circulating lymphocyte count compared with antithymolimus-treated patients. Both agents were equally effective in preventing acute rejection.

See Table 8 and 11 legends for expansion of abbreviations.

to lymphocyte immune globulin, ATGs from horse, or other equine protein products.²¹⁴ ATG (equine) is classified as category C, and adverse effects on the infant cannot be excluded during breast-feeding.²¹⁴ According to production information for ATG,²¹⁴ significant adverse reactions to ATG (equine) include anaphylaxis; dyspnea; pulmonary edema; hemolysis; leukopenia; sepsis or sepsis syndrome; and, on occasion, serum sickness due to the equine immunoglobulin. Chest pain or back pain may indicate the onset of either anaphylaxis or hemolysis. Tachycardia, hypertension, and peripheral edema are commonly observed during administration of this agent. Thrombophlebitis and rash may also occur. Thrombocytopenia is present in roughly one-third of patients. Nausea and diarrhea are also observed with fair frequency. Acute renal dysfunction related to serum sickness may occur, and various degrees of nephrotoxicity are present in about 10% of patients. Liver toxicity is uncommonly reported. Immunosuppression-related infections are noted complications. Immunosuppression-related malignancies occur more frequently in these patients and include non-Hodgkin's lymphoma in male patients and both non-Hodgkin's lymphoma and carcinomas of the cervix, vagina, and vulva in female patients receiving this agent.

Major adverse reactions to ATG (rabbit) include fever, hyperkalemia, hypertension, CMV infection, leukopenia, peripheral edema, sepsis and sepsis syndrome, shivering, tachyarrhythmia, and thrombocytopenia. Injection site reactions, skin rash, and pruritus may occur during use. Nausea and abdominal pain are present in roughly one-third of patients during use. Dyspnea occurs in one-fourth of patients, but ARDS is much less common. Transient liver function abnormalities are rarely observed. Antibodies to rabbit ATG can be documented in virtually all patients and may limit the efficacy of this agent over time in an individual patient. General asthenia and headaches are extremely common during administration of this product. Nephrotoxicity and serum sickness appear to occur fairly uncommonly with use of this agent. Potential increased risk for malignancies, including non-Hodgkin's lymphoma, has been suggested. As with all immunosuppression medications, increased risk for infections occurs with use of this agent.

ATG works in combination with other immunosuppression agents in the posttransplant setting. As such, rabbit or equine ATG exert additive effects on inducing leukopenia and lymphopenia, and in some cases, thrombocytopenia can occur. ATG will reduce the effectiveness of live virus and other vaccines. The ATG preparations can also induce unreliability in laboratory testing for blood cross-match or panel-reactive antibody cytotoxicity assays because of assay

interference. In addition, rabbit antibody-based serum immunoassay results may be unreliable during ATG (rabbit) therapy.

3.3.2.2 Pregnancy Classification—No adequate, well-controlled studies of ATG administered to pregnant women exist. The FDA has designated ATG as category C for all trimesters, and it should only be used during pregnancy if clearly necessary.²¹⁴ There are insufficient data to establish its safety in breast-feeding.

3.3.2.3 Monitoring—Doses are adjusted following three-times-weekly assays to target sheep erythrocyte rosette levels of circulating mononucleated cells to <10%. Alternative dose adjustment monitoring approaches are aimed at maintaining CD3 counts of <20/ μ L and CD2 counts <50/ μ L.^{213,215}

Considerations for clinicians regarding ATG for patients with lung disease and lung transplant recipients:

- *Monitoring the administration of the drug:* Monitoring for infusion reactions should be undertaken during drug infusion (eg, pulmonary edema, SIRS).
- *Monitoring blood work:* CBC count and hepatic and renal function should be monitored periodically as patients are receiving therapy. Daily CBC count and hepatic and renal function laboratory results should be obtained during the initiation of therapy, and subsequent intervals of testing will depend on clinical response. If reinstitution of therapy is considered following prior exposure, laboratory evaluation for host antibodies (where available) before reinstitution of therapy should be considered.
- *Monitoring of drug clearance:* Doses may be adjusted following thrice-weekly assays to suppress sheep erythrocyte rosette levels of circulating mononucleated cells to <10%. Alternative dose adjustment monitoring approaches are aimed to maintain CD3 counts of <20/ μ L and CD2 counts of <50/ μ L.
- *Monitoring for drug/drug interaction:* ATG frequently is used in combination with other immunosuppressive agents. Therefore, additive or synergistic suppression of host immunity (particularly lymphocyte-based defenses) can occur when this agent is used with other immunosuppressive therapies.
- *Prophylaxis against infections:* ATG increases the risk for certain infections, such as atypical bacterial infection; fungal infections, including *Pneumocystis pneumonia*; and viral infections, including CMV. Prophylaxis for *Pneumocystis*

pneumonia should be considered in all patients. Careful monitoring for other infections should be implemented in all patients.

The following topics have been identified for prioritization for future research regarding ATG antibodies:

- *How frequently one needs to monitor CBC count and hepatic function.*
- *The appropriate medications useful for preventing or minimizing infusion reactions.*

Information for patients:

- *Adverse events associated with antilymphocyte antibody infusions include fever, low BP, and shortness of breath.*

3.3.3 Muromonab: Muromonab has received FDA approval for treatment of steroid-resistant heart transplant rejection, steroid-resistant liver transplant rejection, and renal transplant rejection.²¹⁶⁻²¹⁸ Muromonab has been used in non-FDA-approved indications for lung transplant rejection and prophylaxis, where the evidence supports a favorable outcome in these clinical situations.²¹⁶⁻²¹⁸ Muromonab-CD3 is almost always used in combination with other immunosuppressive agents.²¹⁶⁻²¹⁸ Table 18 summarizes three studies in which toxicity information is available regarding muromonab.^{171,219,220}

3.3.3.1 Toxicity—According to Keay et al²²¹ and product information for Muromonab,²²² muromonab

use is contraindicated during pregnancy (category C) or during breast-feeding. Serious major adverse drug effects include anaphylaxis; pulmonary edema; blindness or visual impairment, which may be irreversible; encephalopathy; increased risk of infections; serious inflammatory disorders (involving the CNS and cardiovascular and respiratory systems); enhanced risk of neoplastic disease; neurologic disorders (generalized and partial seizures, encephalopathy, headache, tremor, dizziness, and confusion); and depressive symptoms. Hypotension, hypertension, and tachycardia occur frequently during administration. Rash and pruritus can be observed. Extremely high fever (temperature in excess of 107°F [41.7°C]) can occur during administration of the first dose. Nausea, vomiting, and diarrhea are present in roughly one-third of treated patients. Coagulation disorders, including acute arterial thrombosis and pancytopenia, have been reported. Antibodies to muromonab will develop in a large portion of treated patients and may limit the effectiveness of this agent over time. Cytokine release syndrome with pulmonary edema may occur with administration and may be prevented or reduced in severity by pretreatment with corticosteroids, antihistamines, and acetaminophen.^{221,222} The use of muromonab has been associated with immunosuppression-related neoplasms. Additionally, accumulating evidence indicates an increased incidence of posttransplant lymphoproliferative disorder in patients who receive muromonab-CD3.^{221,222} The use of this agent has also been associated with fungal, viral, and bacterial infections. In particular, an increased incidence of CMV infection has been observed.

Table 18—Monitoring of Muromonab

Author/Year	Disease	Dose	Route	No. Patients Treated	Study Design	Complications Noted	Comments
Boland et al ²¹⁹ /1993	Posttransplant CMV infection	NA	NA	106 kidney; 33 heart	Cohort	OKT3 or ATG treatment influenced the occurrence of CMV infection in patients with CMV (CI, 1-34; $P = .04$)	OKT3 treatment was given less often in patients with CMV infection ($P < .01$ for overall patients).
Shennib and Auger ¹⁷¹ /1994	Lung transplant with CF	60 mg bid	NA	20 OKT3; 21 no OKT3	Case control	Rejection: 73 OKT3 vs 28 steroid ($P < .005$); cytokine release syndrome in four OKT3 patients; other: polyarthralgia, myalgia skin rash Infection: six patients (aspergillosis, <i>Pseudomonas</i> , CMV pneumonia); PTLD: two patients	OKT3 may be useful in treatment of rejection of grade III or higher.
Portela et al ²²⁰ /1995	Orthotopic lung transplant	5 mg/d $\times$ 10 d	IV	209	Cohort	2.6% lung CMV involvement; risk factor: use of OKT3 posttransplant ($P = .001$) (17 of 26 developed CMV infection)	OKT3 is a significant risk factor for symptomatic CMV infection ($P = .03$).

OKT3 = muromonab CD3. See Table 7, 11, 12, and 15 legends for expansion of other abbreviations.

Muromonab is a potent immunosuppressive drug. It works in combination with other immunosuppressive agents in the posttransplant setting.^{221,222} As such, they exert additive effects on inducing leukopenia; lymphopenia; and, occasionally, thrombocytopenia.^{221,222} Muromonab will reduce the effectiveness of live virus and other vaccines.^{221,222} Additional data suggest that *Echinacea* preparations may decrease the effectiveness of muromonab-CD3. Patient-based investigations have documented an increase in granulocytes, monocytes, and lymphocytes in response to treatment with *Echinacea* preparations,²²³ increased phagocytic activity,²²⁴⁻²²⁶ and increased natural killer cell function.^{221,222}

3.3.3.2 Pregnancy Classification—No adequate, well-controlled studies of muromonab administered to pregnant women exist. The FDA has designated muromonab as category C for all trimesters, and it should only be used during pregnancy if clearly necessary.²²² There are insufficient data to establish its safety in breastfeeding, but the manufacturer considers the use of muromonab in nursing women to be contraindicated because of the potential for serious adverse effects.²²²

3.3.3.3 Monitoring—The manufacturer recommends monitoring of hematologic parameters, renal function, and hepatic function prior to and during therapy, and body weight and chest radiographs should be monitored within 24 h of administration.²²² Plasma levels of muromonab and concentration of plasma CD3⁺ T cells can be followed.²²²

Considerations for clinicians regarding muromonab for patients with lung disease and lung transplant recipients:

- *Monitoring the administration of the drug:* Monitoring for infusion reactions should be undertaken during drug infusion (eg, pulmonary edema, SIRS).
- *Monitoring blood work:* CBC count and hepatic and renal function should be monitored periodically as patients are receiving therapy. Daily CBC count and hepatic and renal function laboratory results should be obtained during the initiation of therapy, and subsequent intervals of testing will depend on clinical response. If reinstitution of therapy is considered following prior exposure, laboratory evaluation for host antibodies (where available) before reinstitution of therapy should be considered.
- *Monitoring of drug clearance:* Doses may be adjusted following thrice-weekly assays to suppress sheep erythrocyte rosette levels of circulating mononucleated cells to <10%. Alternative dose adjustment monitoring approaches are aimed

to maintain CD3 counts of <20/ μ L and CD2 counts of <50/ μ L.

- *Monitoring for drug/drug interaction:* Muromonab frequently is used in combination with other immunosuppressive agents. Therefore, additive or synergistic suppression of host immunity (particularly lymphocyte-based defenses) can occur when this agent is used with other immunosuppressive therapies.
- *Prophylaxis against infections:* Muromonab increases the risk for certain infections, such as atypical bacterial infection; fungal infections, including *Pneumocystis pneumonia*; and viral infections, including CMV. Prophylaxis for *Pneumocystis pneumonia* should be considered in all patients. Careful monitoring for other infections should be implemented in all patients.

The following topics have been identified for prioritization for future research regarding muromonab antibodies:

- *How frequently one needs to monitor CBC count and hepatic function.*
- *The appropriate medications useful for preventing or minimizing infusion reactions.*

Information for patients:

- *Adverse events associated with antilymphocyte antibody infusions include fever, low BP, and shortness of breath.*

3.3.4 Rituximab: Rituximab has regulatory approval for the treatment of CD20⁺ non-Hodgkin's lymphoma and refractory rheumatoid arthritis. Rituximab has also been used to treat chronic lymphoid leukemia, immune (idiopathic) thrombocytopenic purpura, and Waldenström macroglobulinemia.²²⁷ The successful use of rituximab in reducing allosensitization in patients waiting for a transplant has been reported.^{228,229} Rituximab is used in the treatment of posttransplant lymphoproliferative disorder (PTLD), a serious complication of solid organ transplantation that lung transplant recipients are particularly at risk to develop.²³⁰⁻²³⁵ A summary of adverse events associated with rituximab is presented in Tables 19 and 20.^{228-231,234-236} A summary of evidence supporting recommendations for the monitoring of rituximab in patients with lung disease or lung transplant recipients is provided in Table 21. This table summarizes seven studies in which rituximab toxicity has been reported.²³⁰⁻²³⁶

3.3.4.1 Toxicity—Fatal infusion reactions have been reported, primarily with the first infusion.²³⁷ These reactions are characterized by hypoxia, pulmonary infiltrates, respiratory distress, myocardial infarction, ventricular fibrillation, and cardiogenic shock. When

Table 19—Monitoring of Rituximab (Adverse Events)

Author/Year	Fever	Myalgias	Other: Moderate or Serious Infection
Oertel et al ²³⁶ /2005	1/17	None or NR	2/17
Blaes et al ²³⁰ /2005	None or NR	None or NR	5/11
Reams et al ²³⁴ /2003	None or NR	None or NR	1/4
Verschuuren et al ²³⁵ /2002	None or NR	None or NR	1/3
Choquet et al ²³¹ /2006	None or NR	1/46	None or NR

See Table 6 legend for expansion of abbreviation.

used for treatment of PTLT, the infusion is well tolerated, with minor toxicity reported.^{230,236}

In spite of the major effect of rituximab on B cells, little is known about its effect on the immune system. Antibody responses to recall antigens are dramatically lower in patients treated with rituximab.²³⁸ Fatal sepsis was reported in two lung transplant patients being treated for PTLT with rituximab.^{234,235} One of these cases was particularly notable in that hypogammaglobulinemia developed following rituximab treatment.²³⁵ Additionally, rituximab use has been implicated in the deaths of two individuals with systemic lupus erythematosus.²³⁹ Death was caused by progressive multifocal leukoencephalopathy in both cases. Reactivation of Jakob-Creutzfeldt virus that is latent in 80% of adults causes progressive multifocal leukoencephalopathy. The package insert warns about the possibility of reactivation of viral infections.²³⁷

Serum sickness has been reported when rituximab has been used to treat a variety of autoimmune diseases.²⁴⁰⁻²⁴⁴ The incidence of serum sickness may be higher in pediatric patients with idiopathic thrombocytopenic purpura (ITP) than in other rituximab-treated patients.^{240,244}

Interstitial pneumonitis has been reported in several patients with non-Hodgkin's lymphoma.²⁴⁵⁻²⁴⁷ Recovery of lung function has occurred with ceasing rituximab treatment and steroids,²⁴⁵ but other reported cases were fatal.^{246,247}

A meta-analysis demonstrated that neutropenia and increased risk for infection have been encountered with long-term rituximab therapy.²⁴⁸ The risk for neu-

tropenia is higher if the patient has previously or concurrently received cytotoxic chemotherapy.^{248,249}

3.3.4.2 Pediatrics—No systematically gathered information on the safety and efficacy of rituximab in pediatric transplant patients is available. Rituximab has been used in the treatment of PTLT, autoimmune hematologic disorders, and ITP in children.²²⁹

A case series of 13 children with PTLT following solid organ transplantation, including one lung transplant patient, has been published.²²⁹ Mild to moderate infusion reactions were reported.

A phase 1 and 2 study of rituximab in the treatment of ITP in 36 children reported mild infusion-related chills, fever, and respiratory symptoms in 47% of patients receiving their first dose.²⁴⁰ Two patients developed serum sickness, and another developed hypotension.

3.3.4.3 Pregnancy Classification—There are no adequate or well-controlled studies in pregnant women, and rituximab is pregnancy category C.²³⁷ Treatment of a pregnant woman with rituximab for Burkitt lymphoma has been reported.²⁵⁰ Treatment was initiated at 16 weeks gestation.²⁵⁰ Courses of cyclophosphamide, doxorubicin, vincristine, and prednisone were used to induce complete response later in gestation.²⁵⁰ Both the mother and the infant had high rituximab serum concentrations and no B cells at the time of birth.²⁵⁰ The infant had normal B-cell counts and IgG concentrations by age 4 months.²⁵⁰ No studies of rituximab use in lactation have been published. IgG is present in human milk, but the rituximab concentrations in milk and infant absorption of the drug have not been measured.

Table 20—Monitoring of Rituximab (Other Adverse Events)

Side Effect	Incidence	Author/Year	Monitoring Used	Author/Year
Infusion reaction	1/17 to 1/11	Blaes et al ²³⁰ /2005 Oertel et al ²³⁶ /2005	Vital signs	Blaes et al ²³⁰ /2005
Fatal infection	5/11 to 0/38	Blaes et al ²³⁰ /2005 Choquet et al ²³¹ /2006 Reams et al ²³⁴ /2003 Verschuuren et al ²³⁵ /2002 Oertel et al ²³⁶ /2005	NA	NA
Bowel perforation at site of PTLT involvement	1/46	Choquet et al ²³¹ /2006	Safety, tolerability	Choquet et al ²³¹ /2006

See Table 7 and 15 legends for expansion of abbreviations.

Table 21—Monitoring of Rituximab

Author/Year	Study Design	Disease	Dose	No. Patients Treated	Age, y	Duration of Therapy	Duration of Monitoring	Monitoring Used	Complications Noted	Study Adequacy	Comments
Oertel et al ²³⁶ /2005	Open, prospective, MC	PTLD	375 mg/m ² 1, 8, 15, and 22 d	17 (4 lung transplant patients)	33-73	4 wk	Mean, 24.2 mo (range, 0-47 mo)	Graded with WHO criteria	No grade 3 or 4 toxicities	NA	Death from BO and death from <i>Aspergillus</i> pneumonia following complete response to rituximab
Cook et al ²³² /1999	Retrospective, CS	PTLD	Standard regimen	3 lung transplant patients	16-67	Not stated	6-23 mo	Not stated	None described	NA	Death from BO and death from EBV-positive lymphoma
Milpied et al ²³³ /2000	Retrospective, MC	PTLD	375 mg/m ² /wk for 4 wk	38 (3 lung and 1 heart-lung transplant patients)	3-67	4 wk	1-16 mo	Graded with WHO criteria	No grade 3 or 4 toxicities	NA	Eight deaths from PTLT; three deaths from intercurrent disease following complete response
Choquet et al ²³¹ /2006	Prospective, MC	PTLD	375 mg/m ² 1, 8, 15, and 22 d	46 (4 lung and 3 heart-lung transplant patients)	13-73	4 wk	360 d	Graded with WHO criteria	No grade 3 or 4 toxicities; serious adverse effects deemed related: bowel perforation and purpura with myalgia	NA	Nineteen deaths (13 PTLT; two septic shock; one each bronchospasm, chemotherapy toxicity, and acute rejection)
Verschuuren et al ²³⁵ /2002	Retrospective, CS	PTLD	375 mg/m ² /wk for 4 wk	3 lung transplant patients	52-60	4 wk	7-16 mo	Not stated	HGG in one case	NA	One death from invasive aspergillosis
Reams et al ²³⁴ /2003	Retrospective, chart review	PTLD	375 mg/m ² /wk for 4 wk	10 lung transplant patients; 4 treated with rituximab	37-64	2-4 cycles, depending on response	Not stated	Not stated	One patient with multiple infectious complications and small bowel obstruction; no other complications following treatment	NA	One death from multiple infections
Blaes et al ²³⁰ /2005	Prospective, MC	PTLD	375 mg/m ² /wk for 4 wk; repeated every 6 mo up to 4 cycles	11 (5 lung transplant patients)	43-69	4 wk-2 y	Up to 32 mo	Not stated	Infusion-related hypotension and one infusion-related mild HTN	NA	All five lung transplant patients died (three of pneumonia, one of hemorrhage, and one of ARDS and aspergillosis)

EBV = Epstein-Barr virus; HGG = hypogammaglobulinemia; WHO = World Health Organization. See Table 7, 9, 10, and 15 legends for expansion of other abbreviations.

3.3.4.4 Monitoring—No prospective studies to determine superior methods of monitoring patients receiving rituximab are available, and the studies available did not detail their monitoring routines.

Considerations for clinicians regarding rituximab for patients with lung disease and lung transplant recipients:

- *Monitoring blood work:* CBC count should be checked prior to each treatment. Patients should have serology results checked for viral hepatitis prior to initiating therapy.
- *Monitoring of drug clearance:* There are no specific recommendations.
- *Monitoring for drug/drug interaction:* Rituximab can be used in combination with other immunosuppressive agents, and as such, additive or synergistic suppression of host immunity, particularly lymphocyte-based defenses, can occur during use of this agent. There is also the potential for more neutropenia when the drug is given with cytotoxic agents, including cyclophosphamide.
- *Prophylaxis against infections:* Rituximab increases the risk for certain infections, especially viral infections such as hepatitis B and C. Careful monitoring for other infections should be implemented in all patients.

The following topics have been identified for prioritization for future research regarding rituximab:

- *How frequently one needs to monitor CBC count.*
- *The appropriate medications useful for preventing or minimizing infusion reactions.*

Information for patients:

- *Infusion of rituximab may cause abdominal pain, diarrhea, nausea, vomiting, muscle soreness, dizziness, headache, peripheral swelling, fever, or shivering; worsening shortness of breath; rapid or irregular heartbeat; fever, chills, or other signs of infection; and increasing confusion.*

Recommendations for the monitoring of antilymphocyte antibodies in patients with lung disease and lung transplant recipients:

3.3a. For patients who undergo antilymphocyte antibody therapy, monitoring for infusion reactions is recommended (Grade 1B).

3.3b. For patients who undergo antithymocyte globulin or muromonab therapy, monitoring of

CBC counts and liver function tests is recommended during therapy (Grade 1B).

3.3c. For patients with lung disease and lung transplant recipients who will undergo antithymocyte globulin or muromonab therapy, laboratory evaluation for host antibodies (where available) before reinstitution of therapy is suggested (Grade 2C).

3.3d. For patients who undergo muromonab therapy, monitoring for pulmonary edema and systemic inflammatory response syndrome during therapy is recommended (Grade 1B).

3.4 IL-2 Receptor Antagonists

3.4.1 Basiliximab: Basiliximab was approved for the prophylaxis of acute organ rejection in patients receiving renal transplantation in 1998, but has been increasingly used in lung transplantation.²⁵¹ This agent has not been indicated for the treatment of acute allograft rejection. Table 22 summarizes adverse reactions reported with basiliximab.²⁵²⁻²⁶³ Table 23 summarizes the use of basiliximab in two studies of lung transplant patients.^{265,266} Table 24 summarizes 16 studies in which the drug was administered for nonpulmonary indications.^{252-263,267-270} These studies were included in the table because they provided significant information regarding toxicity.

3.4.1.1 Toxicity—No prospective, randomized trials of basiliximab have been performed in lung transplant patients. Two have been performed in cardiac transplant recipients, but the majority of prospective, randomized trials have been completed in renal transplant patients. Two multicenter, double-blind, placebo-controlled trials of basiliximab in renal transplant patients described no major adverse events, leading to FDA approval of the medication in 1998.^{252,253}

Although no reports of cytokine release syndrome or anaphylaxis were initially reported, 17 cases of severe acute hypersensitivity reactions, including anaphylaxis, were described in a postmarketing letter from Novartis Pharmaceuticals Corporation in October 2000.²⁷¹ These reactions occur on initial exposure or following reexposure to basiliximab. Patients can develop hypotension, tachycardia, cardiac failure, bronchospasm, pulmonary edema, respiratory failure, urticaria, rash, pruritis, and sneezing.²⁷¹⁻²⁷³ Antichimeric IgE antibodies appear to be responsible for anaphylaxis following retreatment with the medication.²⁷² The IgE antibodies, however, do not recognize daclizumab, a similar genetically engineered murine monoclonal antibody that binds the IL-2 receptor.²⁷³

Common adverse events associated with basiliximab include abdominal pain, vomiting, dizziness, insomnia, edema, hypertension, anemia, dysuria, cough, dyspnea,

Table 22—Monitoring of Basiliximab (Adverse Events)

Author/Year	Disease	Fever	Infection	Hematologic	Cardiac	Renal	Liver/GI	Pulmonary	Neurologic	Endocrine	Malignancy
Melra et al ²⁵⁹ /2005	Heart transplant	48%	84%	Anemia, 68%	HTN, 76% Hypotension, 32% Fluid overload, 40% Edema, 40%	44%	None or NR	None or NR	None or NR	Hyperglycemia, 80%	None or NR
Segovia et al ²⁶² /2006	Heart transplant	1.9	56%	None or NR	None or NR	None or NR	Diarrhea, 1.9%	None or NR	Confusion, 1.9% Headache, 4.2%	None or NR	None or NR
Vitko et al ²⁶⁰ /2005	Kidney transplant or NR	None or NR	42.5% CMV infection, 7.8%	Anemia, 14.4% Leukopenia, 5.9%	None or NR	Increased Cr level, 17% Renal insufficiency, 12.4% UTI, 15%	Diarrhea, 5.9%	None or NR	Tremor, 4.6%	Hyperglycemia, 9.8%	PTLD, 0.7%
Mourad et al ²⁵⁷ /2004	Kidney transplant	38.5% (n = 20)	42.3% (n = 22) CMV infection, 21.2% (n = 11)	Serum sickness, 1.9% (n = 1) Leukopenia, 19.2% (n = 10)	None or NR	None or NR	None or NR	None or NR	None or NR	None or NR	None or NR
Matl et al ²⁵⁶ /2003	Kidney transplant or NR	None or NR	75%	RBC disorders, 0.5% WBC disorders, 1%	3.5% Myocardopericardial and valve, 2.5% Vascular, 8.9%	UTI, 5.9% Renal insufficiency, 2.5%	3.5% Pancreatitis, 2.0%	None or NR	Nervous system, 1.0% Cerebrovascular, 2.0%	Diabetes mellitus, 1.5%	0.5%
Lebranchu et al ²⁵⁴ /2002	Kidney transplant	2%	65% CMV infection, 12%	None or NR	None or NR	Urinary, 4%	GI, 4%	2%	4%	None or NR	None or NR
Kahan et al ²⁶⁴ /1999	Kidney transplant or NR	None or NR	75% CMV infection, 6.9%	None or NR	None or NR	None or NR	None or NR	None or NR	None or NR	None or NR	Breast carcinoma, 1%
Nashan et al ²⁵² /1997	Kidney transplant	None or NR	85% CMV infection, 20.5%	None or NR	None or NR	None or NR	None or NR	None or NR	None or NR	None or NR	PTLD, 0.6% Malignancy, 1.7%
Spada et al ²⁶³ /2006	Pediatric Liver transplant	None or NR	50%	None or NR	None or NR	HTN, 8.3% Renal failure 8%	None or NR	None or NR	None or NR	None or NR	PTLD, 3%
Neuhaeus et al ²⁵⁵ /2002	Liver transplant	None or NR	80.3% Fungal infection, 16.5%	None or NR	None or NR	None or NR	None or NR	None or NR	None or NR	None or NR	PTLD, 1% Malignancy, 2.6%

(Continued)

Table 22—Continued

Author/Year	Disease	Fever	Infection	Hematologic	Cardiac	Renal	Liver/GI	Pulmonary	Neurologic	Endocrine	Malignancy
Pageaux et al ²⁵ /2004	Liver transplant	None or NR	CMV infection, 54.8%	None or NR	None or NR	HTN, 28.6%	34.5% Hepatitis C recurrence, 63.6%	None or NR	28.6% Psychiatric disorders, 14.3%	Diabetes mellitus, 14.3%	2.4%
Grenda et al ²⁶ /2006	Pediatric kidney transplant	None or NR	Bacterial infection, 32% Viral infection, 15.2%	Anemia, 15.2%	None or NR	Toxic nephropathy, 14.1% Increased Cr level, 30.3% ATN, 12.1% HTN, 34.3% UTI, 19.2%	Diarrhea, 19.2% Vomiting, 10.1% Abdominal pain, 11.1%	Bronchitis, 11.1%	None or NR	Hyperglycemia, 10.1%	None or NR

ATN = acute tubular necrosis; UTI = urinary tract infection. See Table 6, 9, 12, and 15 legends for expansion of other abbreviations.

Table 23—Monitoring of Basiliximab in Lung Transplant Patients

Author/Year	Study Design	Disease	Dose	Route	No. Patients	Age, y	Duration of Therapy	Duration of Monitoring	Complications Noted	Study Adequacy	Comments
Borro et al ²⁶ /2005	Prospective comparison to historical control subjects	Lung transplant	20 mg on days 1 and 4	IV	15 (baseline) vs 13 (no induction)	19-67	Days 1 and 4	40 mo	No AEs or infection greater than placebo	NA	Baseline group, higher-risk patients with renal impairment, older age, or surgical risk
Hachem et al ²⁵ /2005	Retrospective cohort comparison to ATG induction	Lung transplant	20 mg on days 0 and 4	IV	82 (baseline) vs 75 (ATG)	Median, 55	Days 0 and 4	33 mo	No AEs; no difference in CMV infection	NA	Baseline group with greater CMV mismatch, reperfusion injury, and duration of mechanical ventilation

See Table 7, 8, 11, and 12 legends for expansion of abbreviations.

Table 24—Monitoring of Basiliximab in Other Organ Transplant Patients

Author/Year	Study Design	Disease	Dose	Route	No. Patients	Age, y	Duration of Therapy	Duration of Monitoring	Complications Noted	Study Adequacy	Comments
Vitko et al ^{269/2005}	OL, parallel group, randomized comparison of basiliximab and tacrolimus; tacrolimus and MMF; and tacrolimus, MMF, and prednisone	Renal transplant	20 mg on days 0 and 4	IV	153 (basiliximab, tacrolimus) vs 151 (tacrolimus, MMF) vs 147 (tacrolimus, MMF, prednisone)	30-56	Days 0 and 4	6 mo	Anemia, diarrhea, and leukopenia CMV reported as SAE lower in basiliximab group UTI, renal dysfunction, hyperglycemia, and tremor also reported	3	...
Kumar et al ^{269/2005}	Randomized, controlled comparison of basiliximab and CsA, MMF and prednisone to basiliximab and CsA, and MMF and prednisone discontinued at day 7	Renal transplant	20 mg on days 0 and 4	IV	32 (basiliximab, CsA, MMF, prednisone) vs 45 (basiliximab, CsA, MMF, prednisone taper)	37-67	Days 0 and 4	24 mo	Hyperglycemia, weight gain, lipid profiles no different between groups	3	First 17 patients in prednisone discontinuation arm; basiliximab on days 60 and 64 also
Mourad et al ^{257/2004}	Open, randomized, MC comparison of basiliximab vs ATG	Renal transplant	20 mg on days 0 and 4	IV	52 (basiliximab, CsA, MMF, steroid) vs 53 (ATG, CsA, MMF, steroid)	33-58	Days 0 and 4	12 mo	Fever (39%), serum sickness (1.9%), CMV infection (21.2%), leukopenia (19.2%), and thrombocytopenia (0%) significantly less than in basiliximab group	2	One case of serum sickness in the basiliximab group not attributed to basiliximab vs four in the ATG group
Matl et al ^{256/2003}	Open, randomized, MC dose comparison of 40 mg basiliximab vs 2 × 20 mg basiliximab	Renal transplant	40 mg on day 0 or 20 mg on days 0 and 4	IV	100 (basiliximab 40 mg) vs 102 (basiliximab 2 × 20 mg)	37-61	Day 0 or days 0 and 4	12 mo	12.4% AE related to medication, possibly transaminitis and nausea Infection in 75% of both groups One death from bronchopneumonia possibly related to basiliximab; no PTLD	3	CsA, AZA, prednisone primary immunosuppression SAE (26.7%); cardiovascular, vascular, urinary system, and GI system disorders most prominent

(Continued)

Table 24—Continued

Author/Year	Study Design	Disease	Dose	Route	No. Patients	Age, y	Duration of Therapy	Duration of Monitoring	Complications Noted	Study Adequacy	Comments
Laven et al ^{25/2003}	Randomized, DB, placebo-controlled, MC comparison of MMF, CsA, and prednisone with or without basiliximab	Renal transplant	20 mg on days 0 and 4	IV	59 (basiliximab) vs 64 (placebo)	43-58	Days 0 and 4	6 mo	11.9% AE related to basiliximab vs 9.4% placebo Incidence of infection, hepatic function, metabolic function, hematologic parameters no different between groups	5	No neoplasm reported and no patient discontinuation because of medication AE
Lebranchu et al ^{25/2002}	Open, randomized, MC comparison of basiliximab, CsA, MMF, and prednisone vs rabbit ATG, CsA, MMF, and prednisone	Renal transplant	20 mg on days 0 and 4	IV	50 (basiliximab) vs 50 (rabbit ATG)	33-57	Days 0 and 4	6 mo	24% AE related to basiliximab vs 86% rabbit ATG Fever, leukopenia significantly less in basiliximab group Infections less (65%) in basiliximab group 12% (basiliximab) vs 38% (rabbit ATG) developed CMV infection	2	No hematologic or biochemical abnormalities in basiliximab group; no PTLD or neoplasm
Sollinger et al ^{26/2001}	Open, randomized, MC comparison of basiliximab, CsA, MMF, and prednisone vs ATGAM (Pfizer, Inc), CsA, MMF, and prednisone	Renal transplant	20 mg on days 0 and 4	IV	70 (basiliximab) vs 65 (ATGAM)	31-62	Days 0 and 4	12 mo	11% AE related to basiliximab vs 42% ATGAM No cytokine release with basiliximab Infection rate similar (76% vs 77%), including CMV infection (19% vs 17%)	2	ATGAM group: CsA initiated only after Cr level of < 3 mg/dL or fallen by > 50% pretransplant value No PTLD One squamous cell carcinoma in basiliximab group vs three malignancies in the ATGAM group

(Continued)

Table 24—Continued

Author/Year	Study Design	Disease	Dose	Route	No. Patients	Age, y	Duration of Therapy	Duration of Monitoring	Complications Noted	Study Adequacy	Comments
Kahan et al ^{253/1999}	Randomized, DB, placebo-controlled, MC comparison of basiliximab, CsA, and prednisone vs placebo, CsA, and prednisone	Renal transplant	20 mg on days 0 and 4	IV	173 (basiliximab) vs 173 (placebo)	33-58	Days 0 and 4	12 mo	27.2% AE related to basiliximab vs 35.3% AE related to placebo Incidence of infection similar (basiliximab, 75%; placebo, 73%) More HSV infection in placebo group likely because of greater steroid/OKT	5	Safety profile of basiliximab similar to placebo No first-dose infusion-related reactions
Nashan et al ^{252/1997}	Randomized, DB, placebo-controlled, MC comparison of basiliximab, CsA, and prednisone vs placebo, CsA, and prednisone	Renal transplant	20 mg on days 0 and 4	IV	190 (basiliximab) vs 186 (placebo)	18-74	Days 0 and 4	12 mo	No difference in clinical AEs between groups, including infections, laboratory indices, vital signs, and leukocyte or lymphocyte counts Three malignancies in basiliximab group and two in placebo group	5	No cytokine release syndrome One patient developed PTLD in each group at 12 mo
Spada et al ^{265/2006}	Open, randomized comparison of basiliximab and tacrolimus vs tacrolimus and prednisone	Pediatric liver transplant	10 mg (20 mg if >35 kg) on days 0 and 4	IV	36 (basiliximab) vs 36 (prednisone)	1.5-4.3	Days 0 and 4 and 8 (in 13 basiliximab patients)	12 mo	No cytokine release syndrome Infection lower in basiliximab group (50% vs 72%) PTLD in one patient in each group New-onset HTN (16.7% vs 8.3%) higher in prednisone group Patient growth similar between groups	1	Third dose of basiliximab on days 8-10 if fluid loss from abdomen >70 mL/kg Third dose of basiliximab without additional AEs

(Continued)

Table 24—Continued

Author/Year	Study Design	Disease	Dose	Route	No. Patients	Age, y	Duration of Therapy	Duration of Monitoring	Complications Noted	Study Adequacy	Comments
Pageaux et al ²⁵ /2004	Randomized, DB, placebo-controlled comparison of basiliximab, CsA, steroids vs basiliximab, CsA, placebo	Liver transplant	20 mg on days 0 and 4	IV	84 (basiliximab, placebo) vs 90 (basiliximab, steroids)	42-62	Days 0 and 4	6 mo	No difference in AE between groups Basiliximab and placebo AE: GI (34.5%), neurologic (29%), psychiatric (14%), cancer (2.4%), infections (8.3%)	3	Trial of steroids vs steroid withdrawal after day 14 Greater incidence of acute rejection in steroid withdrawal group
Filippini et al ²⁶ /2004	Randomized, DB, placebo-controlled comparison of basiliximab, CsA, AZA, and prednisone or basiliximab, CsA, AZA, and placebo	Liver transplant Hepatitis C +	20 mg on days 0 and 4	IV	66 (basiliximab, placebo) vs 74 (basiliximab, prednisone)	23-65	Days 0 and 4	12 mo	No difference in AE between groups Infection 82% (basiliximab, placebo) vs 87% (basiliximab, prednisone)	5	Hepatitis C recurrence no different between groups Acute rejection higher in placebo group but associated with lower treatment failure rate
Neuhaus et al ²⁵ /2002	Randomized, DB, placebo-controlled comparison of basiliximab, CsA, and steroids vs placebo, CsA, and steroids	Liver transplant	20 mg days 0 and 4	IV	188 (basiliximab, CsA, steroids) vs 193 (placebo, CsA, steroids)	20-72	Days 0 and 4	12 mo	AEs similar between groups Infection rates similar (80% vs 83%) Five nonlymphoma malignancies in basiliximab vs two in placebo Two PTLD in each group No difference in laboratory parameters, vital signs, leukocyte or lymphocyte counts, or kidney function	5	HCV + recipients with more SAE, infections and drug-related AEs

(Continued)

Table 24—Continued

Author/Year	Study Design	Disease	Dose	Route	No. Patients	Age, y	Duration of Therapy	Duration of Monitoring	Complications Noted	Study Adequacy	Comments
Grenda et al ^{[26]/2006}	Randomized, MC, OL comparison of basiliximab, tacrolimus, AZA, and prednisone vs tacrolimus, AZA, and prednisone	Pediatric renal transplant	10 mg (<40 kg) or 20 mg (>40 kg) 0 and 4	IV	99 (basiliximab, tacrolimus, AZA, prednisone) vs 93 (tacrolimus, AZA, prednisone)	2-17	Days 0 and 4	6 mo	Toxic nephropathy (14.1% vs 4.3%) and abdominal pain (11.1% vs 2.2%) more significant in basiliximab group Nephropathy resolved in 13 of 14 with reduction in tacrolimus dosing Infections similar Headache, 4.2% Diarrhea, 1.9% Other (fever, confusional state), 4.2%	3	No solid tumors reported Two patients in nonbasiliximab group developed PTLID vs 0 in basiliximab group
Segovia et al ^{[26]/2006}	Randomized, MC, comparison with OKT3	Heart transplant	20 mg days 0 and 4	IV bolus	48 (basiliximab) vs 51 (OKT3)	45-67	Days 0 and 4	12 mo	No difference in AE, SAE, and infection between groups Anemia, fever, edema, hyperglycemia, fluid overload, renal impairment, HTN, and hypotension No cytokine release syndrome or malignancy noted	3	AEs and infection greater in OKT3 group; efficacy without difference
Mehra et al ^{[25]/2005}	Randomized, MC, DB, placebo controlled	Heart transplant	20 mg days 0 and 4	IV bolus	25 (basiliximab) vs 31 (placebo)	43-66	Days 0 and 4	12 mo	No difference in AE, SAE, and infection between groups Anemia, fever, edema, hyperglycemia, fluid overload, renal impairment, HTN, and hypotension No cytokine release syndrome or malignancy noted	5	Saturation threshold exceeded for 38 ± 13 d No antiidiotype antibodies found

HCV = hepatitis C virus; HSV = herpes simplex virus. See Table 5, 7-9, 11-13, 15, and 18 legends for expansion of other abbreviations.

candidiasis, CMV infection, and fever.²⁷⁴ Additionally, tacrolimus trough concentrations have been noted to be higher in renal transplant patients receiving basiliximab. Tacrolimus dose adjustments may be required throughout the early posttransplant period as the biologic effects of basiliximab diminish.²⁷⁵

3.4.1.2 Pediatrics—Basiliximab is dosed at 10 mg IV on days 0 and 4 after transplant in pediatric patients who weigh < 35 kg. Patients who weigh > 40 kg should receive 20 mg IV, which is similar to adult dosing.²⁷⁶ A case report has been published on basiliximab therapy in two infants who received lung transplants for interstitial pneumonia.²⁷⁷ Adverse events are not described.

Two randomized, multicenter trials have been published in the pediatric population, one each in renal and liver transplantation.^{261,263} Toxic nephropathy (14.1% vs 4.3%) and abdominal pain (11.1% vs 2.2%) were noted at significantly greater rates in the basiliximab group.²⁶¹

An open-label pharmacokinetic/pharmacodynamic safety study evaluating basiliximab in 41 pediatric renal transplant patients aged 1 to 17 years has been published.²⁷⁶ The most common adverse events were hypertension, hypertrichosis, and rhinitis (49% each); urinary tract infection (46%); fever (39%); upper respiratory infection (29%); and sepsis and constipation (24% each).²⁷⁶ Three serious adverse events were possibly medication related and included fever, enteritis, and CMV infection. Six patients (15%) experienced adverse events suspected to be basiliximab related. Biochemical and hematologic abnormalities were low except for reduced magnesium levels (56%), elevated serum uric acid and potassium levels (20% each), and leukocytosis (51%).²⁷⁶

3.4.1.3 Pregnancy Classification—There are no adequate studies on the use of basiliximab in pregnant women. It is classified as pregnancy category B. It is not known whether basiliximab is excreted in human milk. No mutagenic potential has been observed on in vitro assay, and no long-term or fertility studies in laboratory animals have been performed.²⁷⁴

3.4.1.4 Monitoring—According to the product information for basiliximab,²⁷⁸ acute hypersensitivity reactions, including anaphylaxis, have been described in renal transplant patients with early graft loss or when the transplant was abandoned and is more prevalent on repeat exposure or in patients in whom concomitant immunosuppression was discontinued prematurely. Basiliximab may elevate serum levels of tacrolimus. Basiliximab is a chimeric humanized murine monoclonal antibody that binds to IL-2 receptors (CD25) on activated lymphocytes, thereby inhibiting lymphocyte differentiation and proliferation. Although rare, life-threatening hypersensitivity reactions leading to anaphylaxis during basiliximab infusion can occur.

Medication side effects have otherwise been reported to be no greater than those in transplant patients receiving maintenance immunosuppression alone.²⁷⁸

Considerations for clinicians regarding basiliximab for patients with lung disease and lung transplant recipients:

- *Monitoring the administration of the drug:* Patients should be observed during the infusion (inpatient or outpatient infusion center) with frequent monitoring of vital signs and have close follow-up for 24 to 48 h after the infusion.
- *Monitoring blood work:* CBC count and creatinine level should be checked within 24 to 48 h following the infusion. Daily CBC count and hepatic and renal function laboratory results should be obtained during the initiation of therapy, and subsequent intervals of testing will depend on clinical response.
- *Monitoring of drug clearance:* This is not applicable.
- *Monitoring for drug/drug interaction:* Live vaccines should not be administered to patients being treated with basiliximab. The immune response to inactivated vaccines may be poor.
- *Prophylaxis against infections:* No specific recommendations are available.

The following topics have been identified for prioritization for future research regarding basiliximab:

- *The need for infection prophylaxis and monitoring for infection.*
- *Requirements for monitoring drug administration.*

Information for patients:

- *Check your temperature frequently and report a fever to your physician immediately.*
- *Report to your physician signs of infection, such as cough, aches, fever, and chills; a wound or cut with redness, pain, discharge, or pus; pain; burning with urination; and nausea, vomiting, and diarrhea.*
- *Report shortness of breath or other changes in your breathing to your physician.*

3.4.2 Daclizumab: Daclizumab was approved in 1997 for acute organ rejection prophylaxis in renal transplant patients but has been increasingly used in lung transplantation.²⁵¹ This agent has not been indicated for the treatment of acute allograft rejection. Studies reporting adverse reactions associated with the use of daclizumab are presented in Table 25.²⁷⁹⁻²⁹² Table 26 summarizes six studies using daclizumab for

Table 25—Monitoring of Daclizumab (Adverse Events)

Author/Year	Disease	Fever	Infection	Hematologic	Cardiac	Renal	Liver/GI	Pulmonary	Neurologic	Endocrine	Malignancy
Beniaminovitz et al ²⁸³ /2000	Heart transplant	None or NR	CMV, 25%	None or NR	None or NR	Pyelonephritis, 3.6%	Gastroenteritis, 3.6%	Pneumonia, 3.6%	Steroid psychosis, 3.6%	Hip pain, 3.6%; Hip replacement, 3.6%	None or NR
Hershberger et al ²⁸⁷ /2005	Heart transplant	None or NR	Opportunistic infection, 33% (CMV, 20%; <i>Candida</i> , 9.3%; HSV, 5.6%; HZV, 4.2%; cryptococcus, 0.5%) Mortality, 15% (because of serious infection in those who received cytolytic therapy)	None or NR	None or NR	None or NR	None or NR	None or NR	None or NR	None or NR	5.1% PTLD, 0.5%
Vincenti et al ²⁷⁹ /1998	Kidney transplant	9	Local infection, 47% Viral, 23% Fungal, 17% CMV, 12% Sepsis, 3% Local infection, 56%	None or NR	None or NR	None or NR	None or NR	Pneumonia, 2%	None or NR	None or NR	Lymphoma, 1.6%
Nashan et al ²⁸⁹ /1999	Kidney transplant	12	Viral 30% CMV, 18% Fungal, 9% Bacteremia/sepsis, 6%	None or NR	None or NR	None or NR	None or NR	Pneumonia, 6%	None or NR	None or NR	None or NR
Nair et al ²⁹² /2001	Kidney transplant	None or NR	0.9 episodes/patient	None or NR	None or NR	None or NR	Transaminitis, 7.7%	None or NR	None or NR	Hyperlipidemia, 69%	None or NR
Stratta et al ^{290,290} /2005	Kidney-pancreas transplant	None or NR	At 6 mo, 55% Serious infection at 3 y, 27%	None or NR	None or NR	UTI, 11%	Nausea, 14% Vomiting, 13% Diarrhea, 8%	Pneumonia, 6%	None or NR	None or NR	4.6% (SCCA, bladder, brain, lymphoma) PTLD, 0.5%
Pescovitz et al ²⁸⁴ /2003	Kidney transplant	None or NR	Overall, 20% HSV, 6% CMV, 8%	None or NR	None or NR	None or NR	None or NR	None or NR	None or NR	None or NR	None or NR
Rostaing et al ²⁸⁸ /2005	Kidney transplant	None or NR	None or NR	Anemia, 23.5% Leukopenia, 21.5%	Tachycardia, 2.7%	UTI, 25% Tubular necrosis, 18% HTN, 16% Kidney dysfunction, 15.4%	Diarrhea, 16.5% Jaundice, 1.9%	Pneumonia, 4.2% Dyspnea, 1.9%	None or NR	Hyperglycemia, 13.1% Gout, 1.9%	None or NR

(Continued)

Table 25—Continued

Author/Year	Disease	Fever	Infection	Hematologic	Cardiac	Renal	Liver/GI	Pulmonary	Neurologic	Endocrine	Malignancy
Ciancio et al ²⁸³ /2002	Kidney transplant	None or NR	Requiring hospitalization, 13% (bacteremia, 7%; sepsis, 3%; abscess, 3%)	None or NR	None or NR	HTN, 8.3% Renal failure, 8%	None or NR	None or NR	None or NR	Diabetes, 14%	None or NR
Dresske et al ²⁸⁹ /2006	Kidney transplant	None or NR	CMV, 20% <i>Candida</i> gastritis, 7.5% Wound infection, 5%	Anemia, 28 Leukopenia, 10	None or NR	UTL, 55% HTN, 20%	Diarrhea, 10%	Pneumonia, 5%	Tremor, 7.5%	Cataract, 12.5% Alopecia, 10%	None or NR
Boillot et al ²⁸⁸ /2005	Liver transplant	None or NR	CMV, 5.1% Sepsis, 3.1%	None or NR	None or NR	Renal insufficiency, 27.9% HTN, 13% Renal failure, 2.8%	Liver function abnormalities 17% Jaundice, 12.3%	None or NR	None or NR	Hyperglycemia, 12% Diabetes mellitus, 5.7%	None or NR
Van Assche et al ²⁹² /2006	Ulcerative colitis	12.8	Sinusitis, 12.8% Influenza, 10.6%	None or NR	None or NR	None or NR	Abdominal pain, 12.8% Nausea, 10.6% Colitis, 8.5%	Nasopharyngitis, 12.8% Pneumonia, 3.6%	Headache, 10.6%	Pruritis, 2.1%	None or NR
Lee et al ²⁸⁵ /2004	GVHD	None or NR	Severe infection, 25%	None or NR	None or NR	None or NR	None or NR	None or NR	None or NR	None or NR	None or NR

GVHD = graft-vs-host disease; HZV = herpes zoster virus; SCCA = squamous cellular carcinoma antigen. See Table 6, 9, 12, 15, 22, and 24 legends for expansion of other abbreviations.

lung transplant patients.^{218,293-297} Table 27 summarizes 12 studies using daclizumab in other organ transplant patients.^{279,280,282-286,288-292}

3.4.2.1 Toxicity—Although not described specifically in the published literature, severe hypersensitivity reactions, including anaphylaxis, were added to the warning label for daclizumab in 2003.²⁹⁸ This reaction has been observed on initial exposure and following reexposure to daclizumab. Patients may develop hypotension, bronchospasm, wheezing, laryngeal edema, pulmonary edema, cyanosis, hypoxia, respiratory arrest, cardiac arrhythmia, cardiac arrest, peripheral edema, loss of consciousness, fever, rash, urticaria, diaphoresis, pruritus, or injection site reactions.²⁹⁸ Seventeen postmarketing cases of hypersensitivity to basiliximab, a chimeric monoclonal antibody similarly directed to the IL-2 receptor α (IL2RA), were also described in a letter from Novartis Pharmaceuticals Corporation in October 2000.²⁷¹

The use of murine monoclonal IL2RA antibodies is limited in humans because of a short half-life and the immunologic consequences of human antimurine antibodies.²⁹⁹ This remains a concern with daclizumab because 10% of the medication contains murine sequences.

Adverse events reported to be caused by daclizumab $\geq 5\%$ of the time in clinical trials involving other solid organ transplants include constipation, nausea, diarrhea, vomiting, abdominal pain, pyrosis, dyspepsia, edema, tremor, headache, dizziness, chest pain, fever, pain, fatigue, hypertension, hypotension, dyspnea, pulmonary edema, coughing, acne, impaired wound healing, insomnia, musculoskeletal pain, back pain, tachycardia, thrombosis, bleeding, and lymphocytosis.^{203,279,280,282,284,285,288-292,300-303}

3.4.2.2 Pediatrics—The safety and efficacy of daclizumab have been described in pediatric renal, liver, and cardiac transplant studies^{283,301,304,305}; however, none are prospective, randomized trials. Proprietary studies in pediatric patients have established the safety of daclizumab in those aged 11 months to 17 years.³⁰⁰ An open-label study of 60 pediatric renal transplant recipients (median age, 10 years) using daclizumab administered at 1.0 mg/kg every 2 weeks for five doses found a rejection rate of only 17% at 1 year.³⁰⁰ The incidence of anti-daclizumab antibodies was 34% in the first 3 months, which is greater than the 14% previously reported in adults.³⁰⁰ Adverse events noted to occur more frequently in pediatric patients than in the adult population include diarrhea, postoperative pain, fever, vomiting, aggravated hypertension, pruritus, and infections of the upper-respiratory and urinary tracts.³⁰⁰

3.4.2.3 Pregnancy Classification—There are no adequate studies on the use of daclizumab during pregnancy. It is classified as pregnancy category C.

Table 26—Monitoring of Daclizumab for Lung Transplant

Author/Year	Study Design	Disease	Dose	Route	No. Patients Treated	Age, y	Duration of Therapy	Duration of Monitoring	Complications Noted	Study Adequacy	Comments
Brock et al ²³⁵ /2001	Prospective cohort comparison of daclizumab, OKT, and ATG	Lung transplant	1 mg/kg	IV	23 (daclizumab) vs 34 (ATG) vs 30 (OKT)	39-65	Day 0 then every 2 wk × 4	1-15 mo	No adverse effects Lower rate of bacterial infections compared with other groups No fungal infection and less likely to develop viral infection in daclizumab group	NA	Cytokine release 40% in OKT group and thrombocytopenia 74% in ATG group. All CsA, AZA, and prednisone
Garrity et al ²³⁶ /2001	Retrospective comparison with historical control subjects without induction	Lung transplant	1 mg/kg	IV	22 (daclizumab) vs 21 (control)	29-67	Day 0 then every 2 wk × 4	6 mo	No adverse effects All on tacrolimus and AZA or MMF and prednisone	NA	CMV infection (18%), fungal infection (18%), and PTLD (4%) similar between groups
Bhorade et al ²³⁵ /2003	Retrospective comparison of tacrolimus, AZA, and prednisone vs tacrolimus, AZA, prednisone, and daclizumab vs tacrolimus, MMF, prednisone, and daclizumab	Lung transplant	1 mg/kg	IV	32 (tacrolimus, AZA, prednisone) vs 49 (tacrolimus, AZA, prednisone, daclizumab) vs 28 (tacrolimus, MMF, prednisone, daclizumab)	37-61	Day 0 then every 2 wk × 4	Median, 36-42 mo	No adverse effects Three-y infection rates with daclizumab: CMV, 28-32%; <i>Aspergillus</i> pneumonia, 6%-17%; bacterial infection, 17%-22% No difference between groups despite daclizumab	NA	Lower acute rejection at 1 and 3 y in tacrolimus, MMF, prednisone, and daclizumab groups ($P < .05$) but NS when corrected for age and CF
Burton et al ²³⁷ /2006	Retrospective comparison of ATG, CsA, AZA, and prednisone vs daclizumab, CsA, AZA, and prednisone	Lung transplant	1 mg/kg	IV	169 (daclizumab) vs 166 (ATG)	11-71	Day 0 then every 2 wk × 4	Up to 48 mo	No adverse effects CMV infection, 2% PTLD, 2% at 2 y	NA	A2 or greater rejection greater in daclizumab group at 3 mo (83% vs 65%) and 2 y (91% vs 74%) Daclizumab 2-y survival, 64% vs ATG at 79% ($P = NS$)

(Continued)

Table 26—Continued

Author/Year	Study Design	Disease	Dose	Route	No. Patients Treated	Age, y	Duration of Therapy	Duration of Monitoring	Complications Noted	Study Adequacy	Comments
Bhorade et al ²⁹⁶ /2002	Retrospective review of CMV infection and ganciclovir resistance at a single center	Lung transplant	1 mg/kg	IV	92 (daclizumab) + 138 (control)	30-60	Day 0 then every 2 wk × 4	Up to 80 mo	Daclizumab associated with a sevenfold greater likelihood of ganciclovir resistance ($P < .05$)	NA	39% (83 of 212) developed CMV 14% (12 of 83) were ganciclovir resistant Daclizumab associated with a greater number of CMV episodes and ganciclovir exposure All on CsA, AZA, and prednisone Acute rejection no different (daclizumab, 66%; control, 79%; $P = .22$) at 6 mo
Weill et al ²⁹⁶ /2003	Retrospective comparison of ganciclovir with CMV IgG vs ganciclovir alone to prevent CMV infection	Lung transplant	1 mg/kg	IV	38 (daclizumab, ganciclovir, CMV IgG) vs 48 (ganciclovir)	21-66	Day 0 then every 2 wk × 4	At least 6 mo	No AEs CMV disease reduced in CMV IgG group (7.9% vs 33.3%, $P < .008$) despite daclizumab	NA	

See Table 7, 8-13, 15, and 18 legends for expansion of abbreviations.

Increased risk of early prenatal loss has been noted in cynomolgus monkeys when daclizumab was administered to pregnant animals.³⁰⁰ In addition, IgG molecules cross the placental barrier.³⁰⁰ Although it is not known whether daclizumab is excreted in human milk, four of seven lactating cynomolgus monkeys given 10 mg/kg of daclizumab were found to secrete very low levels of the medication (0.17%-0.28% of maternal serum levels) in breast milk.³⁰⁰

3.4.2.4 Monitoring—Daclizumab is a humanized IgG1 monoclonal antibody that binds to IL-2 receptors (CD25) on activated lymphocytes, thereby inhibiting lymphocyte differentiation and proliferation.³⁰⁶ Although rare, life-threatening hypersensitivity reactions leading to anaphylaxis during daclizumab infusion can occur.³⁰⁶ Increased mortality has been noted in cardiac transplant recipients and appears to be related to severe infections and the concomitant use of antilymphocyte antibodies.³⁰⁶ The incidence of antidaclizumab antibody formation is 14% in adult and 34% in pediatric patients.³⁰⁶ The clinical significance of this finding is unknown. Medication side effects have otherwise been reported to be no greater than those in transplant patients receiving maintenance immunosuppression alone. During infusions of daclizumab, vital signs have been monitored for the possibility of acute hypersensitivity reactions, including anaphylaxis.³⁰⁶ This adverse reaction was described after approval of daclizumab and can occur both on initial exposure and following reexposure to the medication.³⁰⁶ A similar warning has been issued for basiliximab, which is a chimeric (murine/human) monoclonal antibody that also binds to the IL2RA chain.³⁰⁷ A detailed description of these reactions involving basiliximab has been published and involves renal transplant patients with early graft loss and is more prevalent on repeat exposure or in patients in whom concomitant immunosuppression was discontinued.²⁷¹⁻²⁷³

Recommendations for the monitoring of IL-2 receptor antagonists in patients with lung disease and lung transplant recipients:

3.4a. For patients who undergo IL-2 receptor antagonist therapy, monitoring for infusion reactions is recommended (Grade 1C).

3.4b. For patients who undergo IL-2 receptor antagonist therapy, monitoring of renal function, CBC counts, and infection is recommended (Grade 1C).

3.4c. For patients who undergo IL-2 receptor antagonist therapy, the simultaneous use of either basiliximab (Grade 1C) or daclizumab (Grade 1B) with antilymphocyte antibodies is not recommended.

Table 27—Monitoring of Dacizumab for Other Organ Transplants

Author/Year	Study Design	Disease	Dose	Route	No. Patients	Age, y	Duration of Therapy	Duration of Monitoring	Complications Noted	Study Adequacy	Comments
Vincenti et al ^{279/1998}	Randomized, DB, placebo-controlled, MC comparison of dacizumab, CsA, AZA, and prednisone with placebo, CsA, AZA, and prednisone	Renal transplant	1 mg/kg	IV	126 (dacizumab) vs 134 (placebo)	34-60	Day 0 then every 2 wk × 4	6 mo	No difference in AE between groups SAE, 5% Fever, 9% Sepsis, 3% Pneumonia, 2% Fungal infection, 17% Local infection, 47% Viral infection, 23% CMV infection, 12%	3	Rejection lower in dacizumab group (22% vs 35%, $P = .03$) Two cases of lymphoma at 1 y in dacizumab group No cytokine release syndrome or acute AE reported
Nashan et al ^{280/1999}	Randomized, DB, placebo-controlled, MC comparison of dacizumab, CsA, and prednisone with placebo, CsA, and prednisone	Renal transplant	1 mg/kg	IV	116 (dacizumab) vs 111 (placebo)	24-54	Day 0 then every 2 wk × 4	6 mo	No difference in AE between groups Survival greater in dacizumab group (99% vs 94%, $P = .01$) Infections similar: local infections, 56%; viral, 30%; CMV, 18%; fungal, 9%; fever, 12%; bacteremia/sepsis, 6%; pneumonia, 6%	3	No PTLD in dacizumab group Rejection lower in dacizumab group (28% vs 47%, $P = .01$)
Nair et al ^{282/2001}	Open, randomized comparison of dacizumab vs basiliximab	Renal transplant	1 mg/kg	IV	13 (dacizumab) vs 10 (basiliximab)	29-49	Day 0 then every 2 wk × 4	Mean, 9.7 mo	No difference in AEs Infection, 0.9/patient Hyperlipidemia, 69%; LFT abnormalities, 7.7% No leukopenia, CMV infection, PTLD, or malignancy	1	Acute rejection, 7.7% All patients on CsA, MMF, and prednisone

(Continued)

Table 27—Continued

Author/Year	Study Design	Disease	Dose	Route	No. Patients	Age, y	Duration of Therapy	Duration of Monitoring	Complications Noted	Study Adequacy	Comments
Stratta et al ^{280,290/2005}	Open, randomized, MC comparison of daclizumab five doses vs daclizumab two doses vs control	Renal-pancreas transplant	1 mg/kg (5 doses) or 2 mg/kg (2 doses)	IV	107 (daclizumab, 5 doses) vs 112 (daclizumab, 2 doses) vs 78 (control)	31-49	Day 0 then every 2 wk × 4 (5 doses) or day 0 then every 2 wk × 1 (2 doses) or no induction	6 mo-3 y	No SAE associated with daclizumab Infections at 6 mo in daclizumab groups, 46% and 55% Serious infection, 20% and 27% at 3 y Ten malignancies in daclizumab groups at 3 y vs 0 in control group One PTLD in daclizumab group No SAE associated with daclizumab Infections similar (20% in daclizumab group) Herpetic (6%) and CMV (8%) at 6 mo vs 0 in placebo Four more cases of CMV in daclizumab group by 12 mo AE greater in daclizumab group: pneumonia (4.2% vs 1.1%) Tachycardia (2.7% vs 0.4%) Cholestatic jaundice (1.9% vs 0%) Gout (1.9% vs 0%) Dyspnea (1.9% vs 0%)	1	Acute rejection of kidney and pancreas combined, 20.6% vs 16.9% vs 30.8% (<i>P</i> = .16 daclizumab 2 doses vs control) Event-free survival, no difference at 3 y (50% vs 56% vs 46%) All patients taking tacrolimus, MMF, and prednisone
Pescovitz et al ^{284/2003}	Randomized, DB, placebo-controlled, MC comparison of daclizumab vs placebo	Renal transplant	1 mg/kg	IV	50 daclizumab vs 25 placebo	44-48	Day 0 then every 2 wk × 4	12 mo	No SAE associated with daclizumab Infections similar (20% in daclizumab group) Herpetic (6%) and CMV (8%) at 6 mo vs 0 in placebo Four more cases of CMV in daclizumab group by 12 mo AE greater in daclizumab group: pneumonia (4.2% vs 1.1%) Tachycardia (2.7% vs 0.4%) Cholestatic jaundice (1.9% vs 0%) Gout (1.9% vs 0%) Dyspnea (1.9% vs 0%)	3	No PTLD Acute rejection similar at 14% daclizumab vs 16% placebo at 12 mo PK of MMF not affected by daclizumab and vice versa
Rostaing et al ^{285/2005}	OL, randomized, MC comparison of daclizumab, tacrolimus, and MMF vs tacrolimus, MMF, and prednisone	Renal transplant	1 mg/kg	IV	260 (daclizumab) vs 278 (control)	34-58	Day 0 then every 2 wk × 1	6 mo	AE greater in daclizumab group: pneumonia (4.2% vs 1.1%) Tachycardia (2.7% vs 0.4%) Cholestatic jaundice (1.9% vs 0%) Gout (1.9% vs 0%) Dyspnea (1.9% vs 0%)	3	Acute rejection similar at 16.5% in both groups, despite corticosteroid-free regimen Patient and graft survival similar Changes in cholesterol and bone density favor daclizumab group

(Continued)

Table 27—Continued

Author/Year	Study Design	Disease	Dose	Route	No. Patients	Age, y	Duration of Therapy	Duration of Monitoring	Complications Noted	Study Adequacy	Comments
Ciancio et al ²⁸³ /2002	OL, randomized comparison of daclizumab, tacrolimus, MMF, and prednisone vs alemtuzumab, tacrolimus, and MMF vs ATG, tacrolimus, MMF, and prednisone	Renal transplant	1 mg/kg	IV	30 (daclizumab) vs 30 (alemtuzumab) vs 30 (ATG)	47-53	Day 0 then every 2 wk × 4	12 mo	No acute medication-related AEs Infections requiring hospitalization similar between groups: Daclizumab, 13% (bacteremia, 2 patients; sepsis, 1 patient; abscess, 1 patient) Posttransplant diabetes, 14% in daclizumab group AE: Anemia, 28% HTN, 20% Cataract, 12.5% Leukopenia, diarrhea, and alopecia, all 10% Tremor, 7.5% Infections: UTI, 55%; CMV, 20%; <i>Candida</i> gastritis, 7.5%; pneumonia and wound, both 5% Lower incidence of posttransplant diabetes mellitus (5.7%), CMV infection (5.1%), and hepatitis (1.1%) in daclizumab group than steroid group. Daclizumab SAE: renal insufficiency, 5.1%; sepsis, 3.1%; renal failure, 2.8%; cMV infection, 1.7%	2	AR (17%) identical between groups Eighty percent of alemtuzumab group steroid free at 12 mo Graft and patient survival similar
Dresske et al ²⁹¹ /2006	OL, randomized comparison of immunosuppression withdrawal for 72 h vs control (daclizumab, tacrolimus, MMF, prednisone) Both groups with daclizumab	Renal transplant	1 mg/kg	IV	20 (immunosuppression withdrawal) vs 20 (control)	35-67	Day 0 then every 2 wk × 4	24 mo	AE: Anemia, 28% HTN, 20% Cataract, 12.5% Leukopenia, diarrhea, and alopecia, all 10% Tremor, 7.5% Infections: UTI, 55%; CMV, 20%; <i>Candida</i> gastritis, 7.5%; pneumonia and wound, both 5% Lower incidence of posttransplant diabetes mellitus (5.7%), CMV infection (5.1%), and hepatitis (1.1%) in daclizumab group than steroid group. Daclizumab SAE: renal insufficiency, 5.1%; sepsis, 3.1%; renal failure, 2.8%; cMV infection, 1.7%	2	Pilot study Immunosuppression withdrawal, 10%; AR, 94.4% steroid withdrawal vs 30% AR; 76.5% steroid withdrawal in control Graft and patient survival similar at 2 y
Boillot et al ²⁸⁶ /2005	OL, randomized comparison of daclizumab, tacrolimus, vs tacrolimus and corticosteroids	Liver transplant	1 mg/kg	IV	356 (daclizumab, tacrolimus) vs 352 (tacrolimus, steroids)	41-61	Days 0 and 7	3 mo	Lower incidence of posttransplant diabetes mellitus (5.7%), CMV infection (5.1%), and hepatitis (1.1%) in daclizumab group than steroid group. Daclizumab SAE: renal insufficiency, 5.1%; sepsis, 3.1%; renal failure, 2.8%; cMV infection, 1.7%	2	AR and graft and patient survival similar between groups Steroid-resistant AR lower in daclizumab group (2.8% vs 6.3%) Daclizumab AE: kidney abnormal, 28%; LFT elevation, 17%; HTN, 12.8%; jaundice, 12.3%; hyperglycemia, 12%; infection, 11.1%

(Continued)

Table 27—Continued

Author/Year	Study Design	Disease	Dose	Route	No. Patients	Age, y	Duration of Therapy	Duration of Monitoring	Complications Noted	Study Adequacy	Comments
Van Assche et al ^{202/2006}	Randomized, DB, placebo-controlled comparison of daclizumab 1 mg/kg × 2 vs 2 mg/kg × 4 vs placebo	Ulcerative colitis	1 mg/kg (2 doses) or 2 mg/kg (4 doses)	IV	56 (daclizumab 1 mg/kg) vs 47 (daclizumab 2 mg/kg) vs placebo	27-61	Day 0 then at 4 wk (2 doses) or day 0 then every 2 wk × 3 (4 doses) or placebo	2 mo	AE similar between groups One patient with infusion reaction resolved SAE 12.5% and 4.3% in daclizumab groups, most because of ulcerative colitis exacerbation Pneumonia in two patients in the 1-mg/kg daclizumab group No laboratory value changes, malignancy, or opportunistic infection	5	Daclizumab treatment no different than placebo Remission 10% placebo vs 2% (daclizumab 1 mg/kg) and 7% (daclizumab 2 mg/kg) AE (daclizumab 2 mg/kg): nasopharyngitis, pyrexia, abdominal pain, and sinusitis, all 12.8%; headache, nausea, and influenza, all 10.6%; colitis, 8.5%; pruritus, 2.1%
Lee et al ^{285/2004}	Randomized, DB, placebo-controlled comparison of daclizumab and steroid vs placebo and steroid	GVHD in bone marrow transplantation	1 mg/kg	IV	53 (daclizumab, steroids) vs 49 (steroids, placebo)	8-65	Days 1, 4, 8 then weekly until day 100	42-100 d	Severe infection, 25% Hospitalization median of 44 d in daclizumab group vs 36 d in control group (<i>P</i> = .04)	3	No difference in GVHD response between groups Significantly worse survival in daclizumab group at 100 d (77% vs 94%; hazard ratio, 2.4)

LFT = lung function test. See Table 5, 8, 9, 11-13, 15, 24, and 25 legends for expansion of other abbreviations.

3.5 Cytotoxic Agents

3.5.1 Azathioprine: Azathioprine has regulatory approval as an adjunct prophylaxis for renal transplant rejection and for treatment of rheumatoid arthritis and granulomatosis with polyangiitis.³⁰⁸ It has also been used for prophylactic treatment of heart, liver, pancreas, and lung transplantation.³⁰⁹⁻³¹⁷ Additionally, azathioprine has been used to treat pulmonary and extrapulmonary sarcoidosis,³¹⁸⁻³²⁰ cryptogenic organizing pneumonia,³²¹ idiopathic pulmonary fibrosis,³²² interstitial lung disease (ILD) associated with systemic sclerosis,^{323,324} and radiation pneumonitis.³²⁵ A summary of 11 studies supporting recommendations for the monitoring of AZA in patients with lung disease and organ transplant recipients is provided in Table 28.^{310-312,314,316,317,320,322-324,326}

3.5.1.1 Toxicity—Common adverse reactions associated with azathioprine include leukopenia,³²⁷ pancreatitis,³²⁸ and hepatitis.³²⁹ Other effects of bone marrow toxicity include thrombocytopenia, anemia, megaloblastic anemia, aplastic anemia, eosinophilia, myelodysplastic syndrome, and fatal acute myeloid leukemia.^{327,330,331} Patients with thiopurine methyltransferase (TPMT) deficiency are much more likely to encounter bone marrow toxicity.³³² The incidence of hepatitis or pancreatitis for patients receiving azathioprine for Crohn's disease ranges from 4% to 17% for both side effects independently,³³³⁻³³⁵ and azathioprine treatments are discontinued in about 10% to 20% of patients because of side effects.^{327,335} Other adverse reactions linked to azathioprine include skin rash; alopecia; nausea; vomiting; hypersensitivity reactions; muscle weakness; interstitial pneumonitis/fibrosis; and risk of lymphoma, skin cancer, and infection. Rarely, azathioprine hypersensitivity reaction can lead to a sepsis-like syndrome.³³⁶

Several drug interactions can occur with azathioprine. Concomitant administration of allopurinol can greatly increase the effect of azathioprine and associated toxicities.³³⁷ The use of angiotensin-converting enzyme inhibitors with azathioprine has been associated with myelosuppression.³³⁸ Patients receiving azathioprine may be at increased risk of infection from administration of live virus vaccines.³³⁹ Inhibitors of TPMT, such as mesalamine, can considerably increase the risk of myelosuppression. Certain agents (alfalfa, black cohosh, *Echinacea*) may attenuate azathioprine effects, and azathioprine may antagonize anticoagulant (warfarin) effectiveness.³⁴⁰ The use of ribavirin for hepatitis C in patients receiving azathioprine has been reported to induce severe pancytopenia.^{341,342}

3.5.1.2 Pregnancy Classification—Azathioprine has not been associated with an increase in birth defects or miscarriages in some studies,^{343,344} but it has been

linked to birth defects in the Danish Birth Registry cohort study³⁴⁵ and to growth retardation in humans³⁴⁶ and in rats.³⁴⁷ Although azathioprine crosses the placenta in humans, concentrations in the fetus are very low.³⁴⁸ Postpartum leukopenia has been observed in children delivered by women treated with azathioprine.³⁴⁹

3.5.1.3 Monitoring—Monitoring of CBC counts every 2 weeks for the first 4 weeks and then monthly thereafter has been recommended.³⁵⁰ Similarly, liver function tests monitored every 2 weeks for the first 4 weeks and then monthly thereafter have been recommended.³⁵⁰

Considerations for clinicians regarding azathioprine for patients with lung disease and lung transplant recipients:

- *Monitoring blood work:* CBC count and hepatic function should be monitored every 1 to 3 months as long as patients are receiving therapy.
- *Monitoring of drug clearance:* Measurement of TPMT may be useful to detect patients at risk for leukopenia from azathioprine, especially those who will receive higher doses or have a history suggestive of TPMT deficiency. The dose may need adjustment according to creatinine clearance.³⁵¹
- *Monitoring for drug/drug interaction:* Allopurinol inhibits the xanthine oxidase pathway. Patients should not receive azathioprine if they are taking allopurinol. Other drug interactions are listed in Table 11.
- *Prophylaxis against infections:* There are no special issues for azathioprine. Prophylaxis recommendations are discussed in Table 12.

The following topics have been identified for prioritization for future research regarding azathioprine:

- *The use of TPMT testing prior to institution of azathioprine therapy.*
- *The need for prophylaxis against P. jirovecii.*
- *How frequently one needs to monitor CBC count and hepatic function.*

Information for patients:

- *Check your temperature frequently and report a fever to your physician immediately.*
- *Report signs of infection to your physician such as cough, aches, fever, and chills; a wound or cut with redness, pain, discharge, or pus; pain; burning with urination; and nausea, vomiting, and diarrhea.*

Table 28—Monitoring of Azathioprine

Author/Year	Study Design	Disease	Dose	No. Patients Treated	Age, y	Duration of Therapy	Duration of Monitoring	Monitoring Used	Complications Noted	Study Adequacy	Coadministered Agents	Comments
Raghu et al ^{32/1991}	PRCT, DB	IPF	Initial: 3 mg/kg/d (max, 200 mg/d)	AZA, 14; placebo, 13	28-85	≥ 12 mo	≥ 12 mo	PFT, clinical (including CBC, LFT)	Pneumonia (n = 2)	3	Prednisone (all)	No episodes of pancytopenia noted; elevated LFTs in one subject
Müller-Quernheim et al ^{32/1999}	OL	Sarcoidosis	Initial: 2 mg/kg/d Maintenance: 100-150 mg/d	11		≥ 22 mo	Up to 73 mo	Clinical evaluation, PFT, BAL	None	1	Prednisolone (all)	No significant side effects caused by AZA
Demedts et al ^{32/2005}	DB, PRCT, PC, MC	IPF	AZA 2 mg/kg/d (all) Prednisone 10 mg/d for months 4-12 (all) NAC 600 mg tid vs placebo	Group 1 (NAC), 80; Group 2 (no NAC), 75	18-75	12 mo	≥ 12 mo	Clinical evaluation, PFT	Respiratory infection, LFT abnormality	3	AZA (all), Prednisone (all)	LFT abnormality: Group 1, 15% Group 2, 18% Bone marrow toxicity: Group 1, 4% Group 2, 13% Respiratory infection: Group 1, 25% Group 2, 32% Abdominal pain: Group 1, 15% Group 2, 9% All AEs: Group 1, 90% Group 2, 89% Three stopped therapy (one each with nausea, leukopenia, and TB)
Dheda et al ^{32/2004}	RS	ILD with SS	Not stated	11 (8 treated ≥ 12 mo)	32-67	≥ 12 mo for 8 subjects	Up to 31 mo	Clinical evaluation, PFT	Nausea, leukopenia, TB	1	Low-dose prednisone	
Hoyles et al ^{32/2006}	PRCT	PF with SS	AZA 2.5 mg/kg/d (max, 200 mg/d)	AZA, 22; placebo, 23	18-75	≥ 12 mo	223-439 d	Clinical evaluation, PFT, HRCT scan	Abnormal LFT (three total; one withdrawn from study)	2	CYC (induction), prednisone	Similar AE rates for AZA vs placebo
Palmer et al ^{310/2001}	PRCT, 2-center, OL	Lung transplant	AZA 2 mg/kg/d	AZA, 38; MMF, 43	≥ 18	≥ 6 mo	≥ 6 mo	Clinical evaluation, TBLBx, PFT	AZA withdrawal in six (vs 13 in MMF group)	3	CsA, corticosteroids	AZA dose reduced in 13 and discontinued in one for leukopenia

(Continued)

Table 28—Continued

Author/Year	Study Design	Disease	Dose	No. Patients Treated	Age, y	Duration of Therapy	Duration of Monitoring	Monitoring Used	Complications Noted	Study Adequacy	Coadministered Agents	Comments
McNeil et al ³¹⁰ /2006	PRCT, OL, MC	Lung transplant	AZA 2 mg/kg/d adjusted for WBC and platelet count	AZA, 159; MMF, 161	18-65	Up to 3 y	Up to 3 y	Clinical evaluation, PFT, TBLBx	Leukopenia, nausea, anemia, sepsis	4	Induction with ATG CsA, corticosteroids	Similar AE profile for AZA vs MMF; no difference in incidence of BOS for AZA vs MMF
Snell et al ³¹⁰ /2006	PRCT, MC, DB	Lung transplant	AZA 1-3 mg/kg/d	AZA, 112; EVL, 101	14-70	Up to 24 mo	Up to 24 mo	Clinical evaluation, PFT	Leukopenia, anemia, thrombocytopenia, infection, dyslipidemia	5	CsA, corticosteroids	Nonfatal SAEs in 48 (43.2%) taking AZA vs 70 (63.1%) taking EVL; drug-related AE in 63 (56.8%) taking AZA vs 89 (80.2%) taking EVL
Eisen et al ³¹⁴ /2005	PRCT, DB, MC	Heart transplant	AZA 1.5-3 mg/kg/d	AZA, 323; MMF, 327	≥ 18	Up to 36 mo	Up to 36 mo	Clinical evaluation, EMCbX	Leukopenia, cardiac dysrhythmias, heart failure, malignancy, diarrhea, esophagitis, infection	5	CsA, corticosteroids	AE, intercurrent illness, laboratory abnormality in 58 of 289 AZA-treated recipients (20.1%) vs 57 of 289 of MMF-treated recipients (19.7%)
Remuzzi et al ³¹⁴ /2007	PRCT, MC	Renal transplant	AZA 100 mg/d for BW < 75 kg, 150 mg/d for BW ≥ 75 kg	AZA, 124; MMF, 124	45 ± 12	Up to 72 mo	Up to 72 mo	Clinical evaluation	Cardiac arrhythmia, cardiac ischemia, cerebrovascular events, infections, malignancy	4	CsA ± corticosteroids	No significant difference in AE rates for AZA vs MMF groups
Wiesner et al ³¹⁷ /2001	PRCT, MC, DB	Liver transplant	AZA 1-2 mg/kg/d	AZA, 287; MMF, 278	≥ 16	≥ 1 y	≥ 1 y	Clinical evaluation, liver biopsy	Leukopenia, other bone marrow suppression, GI infection, GI symptoms	5	CsA, corticosteroids	No significant difference in AE rates for AZA vs MMF groups

BW = body weight; EMCbX = endomyocardial biopsy; EVL = everolimus; HRCT = high-resolution CT scan; ILD = interstitial lung disease; IPF = idiopathic pulmonary fibrosis; NAC = N-acetylcysteine; PF = pulmonary fibrosis; SS = systemic sclerosis; TBLBx = transbronchial lung biopsy. See Table 5, 6, 8, 9, 11, 13, 24, and 27 legends for expansion of other abbreviations.

Table 29—Monitoring of Cyclophosphamide (Adverse Events)

Side Effect	Incidence/1,000	Author/Year	Monitoring Recommended	Author/Year
Unusual infections	0-20	De Groot et al ³⁵² /2005	Grading of AEs; CBC count; measurements of ESR, CRP, serum creatinine, ALT, alkaline phosphatase, albumin, and glucose; dipstick urinalysis; urine microscopy; and nasal swab BVAS, Disease Extent Index, and the Short Form 36 functional questionnaire Cumulative damage (Vasculitis Damage Index) CrCl and ANCA studies and chest and sinus radiography performed at entry CBC every 2 wk at initiation of therapy and monthly thereafter	De Groot et al ³⁵² /2005
More frequent infections	Dose dependent	Tashkin et al ³⁵⁷ /2006		Tashkin et al ³⁵⁷ /2006
Neutropenia	Dose dependent	Tashkin et al ³⁵⁷ /2006		
Thrombocytopenia	Dose dependent	Tashkin et al ³⁵⁷ /2006		NA
Lymphoma and leukemia	No increase to a relative risk of 4.2-5.7	Girling et al ³⁶⁰ /1985		NA
		Knight et al ³⁶² /2004		
Nonlymphomatous malignancies	No increase to relative risk 7.3 for skin cancer	Girling et al ³⁶⁰ /1985		
		Knight et al ³⁶² /2004		
Hematuria, hemorrhagic cystitis, or both	0-127	Tashkin et al ³⁵⁷ /2006	Urinalysis every 2 wk at initiation of therapy and monthly thereafter	Tashkin et al ³⁵⁷ /2006
Bladder cancer	100-160	Talar-Williams et al ³⁶¹ /1996	Urinalysis yearly for life, with hematuria evaluated	Talar-Williams et al ³⁶¹ /1996
		Knight et al ³⁶² /2004		Knight et al ³⁶² /2004

ALT = alanine aminotransferase; ANCA = antineutrophil cytoplasmic antibodies; BVAS = Birmingham vasculitis activity score; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate. See Table 7, 8, and 10 legends for expansion of other abbreviations.

Table 30—Monitoring of Cyclophosphamide in Lung Disease

Author/Year	Study Design	Disease	No. Patients Treated			Duration of Therapy	Duration of Monitoring	Complications Noted	Study Adequacy	Comments
			Route	CYC/Total	Age, y					
Tashkin et al ^{357/2006}	DB, PRCT	Scleroderma ILD	Oral	79/158	29-82	1 y	2 y	Leukopenia, 19 Neutropenia, 7 Hematuria, 10 Pneumonia, 6 Anemia, 4	5	Leukopenia and neutropenia $P < .05$ from placebo
De Groot et al ^{359/2005}	PRCT, CYC and prednisone vs MTX and prednisone	ANCA-associated vasculitis	Oral	49/100	22-78	1 y	18 mo	Leukopenia, 14 Infections, 9 Diabetes, 3 Osteopenia, 1 HTN, 1 Hypersensitivity reaction, 1 Liver dysfunction, 1 Thrombocytopenia and leukopenia more common than placebo No difference in secondary malignancies between CYC and placebo	4	Drug withdrawn if WBC $< 4,000/\mu\text{L}$ One fatal case of CMV pneumonia in CYC group More leukopenia in CYC group ($P < .001$) Pancytopenia and leukemias more common in busulfan arm
Girling et al ^{360/1985}	DB, PRCT CYC vs busulfan vs placebo	Lung cancer following surgical resection	Oral	234/726	NR	2 y	5 y for hematologic 15 y for malignancy		4	
Gonzalez-Lopez et al ^{364/2004}	PRCT	SLE-associated PH	IV	16/34	18-55	6 mo	6 mo	Infections, 87% in CYC vs 55% in enalapril Nausea or vomiting, 81% CYC vs 6% enalapril	3	Drug side effects not blinded Relative risk and CIs for infections and nausea or vomiting different from enalapril Transition at 6 mo to AZA 2.5 mg/kg/d (maximum, 200 mg) MESNA not used Placebo rates of complications NR except for hematuria One malignancy in each group
Hoyles et al ^{364/2006}	DB, PRCT	Scleroderma ILD	IV	22/45	18-75	6 mo	12 mo	Nausea, 8 Mood disturbance, 4 Mouth ulceration, 3 Rash, 3 Abnormal LFTs, 2 Diarrhea, 2 Dyspepsia, 2 Confirmed hematuria in 1 CYC vs 2 placebo	4	

(Continued)

Table 30—Continued

Author/Year	Study Design	Disease	Dose	Route	No. Patients Treated, CYC/Total	Age, y	Duration of Therapy	Duration of Monitoring	Complications Noted	Study Adequacy	Comments Malignancy/Death Pregnancy
Johnson et al ^{355/1989}	PRCT	Cryptogenic fibrosing alveolitis (IPF)	CYC 100-120 mg/d plus prednisolone 20 mg every other day vs prednisolone 60 mg/d reduced gradually to 20 mg every other day	Oral	21/43	NR	3 y	3 y	Hematologic toxicity, 6 Microscopic hematuria resolved after drug cessation, 1 Prednisolone alone group with 1 osteoporosis Diabetes mellitus, 4 Epigastric discomfort, 1 No cases of ILD seen in CYC arm	3	Investigators performing statistical analysis blinded to treatment groups
Scott ^{357/1977}	DB, PRCT Busulfan and CYC vs placebo	Lung cancer postsurgical resection	CYC 200 mg/d for 10 d, 150 mg/d for 1 y, then 75 mg/d for year 2	Oral	192/726	NR	2 y	5 y		3	One patient in placebo arm with ILD All CYC patients did not have radiographs available for review

MESNA = sodium 2-sulfamylethanesulfonate; PH = pulmonary hypertension; SLE = systemic lupus erythematosus. See Table 5, 6, 28, and 29 legends for expansion of other abbreviations.

Table 31—Monitoring of Cyclophosphamide for Other Diseases

Author/Year	Study Design	Disease	Dose ^a	Route	No. Patients Treated	Age, y	Duration of Therapy	Duration of Monitoring	Complications Noted	Study Adequacy	Comments Malignancy/Death Pregnancy
Smyth et al ^{358/1975}	DB, PRCT	RA on fixed-dose prednisone 3-15 mg/d	75 mg/d	Oral	13 of 29	NR	6 mo	6 mo	One with alopecia in CYC arm	3	No hematologic side effects

See Table 5 and 6 legends for expansion of abbreviations.

^aDose administered at time 0, 2 wk, 64 wk, and every 4 wk thereafter, unless otherwise noted.

- Report shortness of breath or other changes in your breathing to your physician.
- Report signs of liver or pancreas dysfunction to your physician such as nausea and vomiting, yellowing of the skin or whites of the eyes, and abdominal pain.

3.5.2 Cyclophosphamide: Cyclophosphamide was first approved in 1959 and has regulatory approval for the treatment of malignant lymphomas, multiple myeloma, leukemias, mycosis fungoides, neuroblastoma, retinoblastoma, and adenocarcinoma of the breast and ovary. Cyclophosphamide has been used in granulomatosis with polyangiitis and other vasculitides³⁵²; extrapulmonary sarcoidosis^{353,354}; and fibrotic lung diseases, including IPF^{355,356} and scleroderma ILD.^{324,357} It is used for a variety of other connective tissue diseases that can have pulmonary manifestations.³⁵⁸ Cyclophosphamide can be administered either daily orally or intermittently intravenously. Both regimens have been used for pulmonary fibrosis. The intermittent IV regimen has similar toxicity as the oral regimen, but the reported rate appears lower.^{324,359} Table 29 summarizes the adverse events encountered with cyclophosphamide.^{352,357,360-362} Table 30 summarizes seven studies of cyclophosphamide for various lung diseases,^{324,352,355,357,360,363,364} and Table 31 summarizes one study in which cyclophosphamide was used for nonpulmonary disease but has important information regarding toxicity.³⁵⁸

3.5.2.1 Toxicity—Hemorrhagic cystitis is seen with cyclophosphamide therapy and can occasionally be severe or fatal. Fibrosis of the urinary bladder may result. Most cyclophosphamide trials have performed urinalysis before initiating the medication because hematuria is a frequent comorbidity of many lung diseases. Bladder toxicity likely occurs from both the cyclophosphamide parent compound and a number of cyclophosphamide metabolites, including acrolein. Therefore, interventions that limit hemorrhagic cystitis include instructions to drink >3 L of water or other fluids daily. Sodium 2-sulfanylethanesulfonate (MESNA) is a medication that binds acrolein and some other cyclophosphamide metabolites in the urinary bladder, limiting toxicity. MESNA may be given orally as a liquid in juice or by IV and most commonly has been used before and immediately after large IV pulse doses of cyclophosphamide. In a recent prospective trial with IV cyclophosphamide or placebo, there was no additional hematuria seen in a scleroderma population without using MESNA.³²⁴

Bladder cancer is increased in individuals who have received cyclophosphamide. Cigarette smoking further increases the risk. Bladder cancer is also increased in frequency in patients taking cyclophosphamide who have had hemorrhagic cystitis. Bladder cancer appears

to be both dose and duration dependent, with at least a twofold increased risk occurring with each 10 g of cumulative drug exposure³⁶⁵ and further increases over time after a 20-g total dose.³⁶¹ Cancers have been known to occur many years following cyclophosphamide cessation. Bladder cancer screening with urinalysis appears to be sufficient to detect cancer as long as patients with hematuria receive additional evaluation.³⁶²

Lymphomas, leukemias, skin cancers, and probably other solid organ malignancies are likely increased in frequency in individuals receiving cyclophosphamide. In a retrospective study of long-term follow-up of patients with granulomatosis with polyangiitis treated with cyclophosphamide, increased cancer incidence was seen for squamous cell skin cancer (OR, 7.3; 95% CI, 4.4-12), leukemias (OR, 5.7; 95% CI, 2.3-12), and malignant lymphomas (OR, 4.2; 95% CI, 4.2-8.3).³⁶² The interpretation of many such studies are complicated by some increase in cancer incidence with the baseline disease state. In a Swedish registry study of 246 patients with scleroderma followed for up to 13 years, no increase in malignancy was seen when comparing cyclophosphamide with other medications.³⁶⁶ In a prospective 15-year evaluation of 726 patients with lung cancer treated with busulfan, cyclophosphamide, or placebo, no additional malignancies were seen in the cyclophosphamide arm above the placebo rate.³⁶⁰

CHF, hemopericardium, and hemorrhagic myocarditis have been seen after high doses of cyclophosphamide. These side effects usually resolve after stopping therapy. Alopecia is common, and hair may return with a different texture or color.

The frequency of bacterial, fungal, viral, and protozoan infections is increased with cyclophosphamide treatment. There is no consensus that prophylaxis for any of these infections is necessary in patients receiving cyclophosphamide, although some case series have used prophylaxis for *P jiroveci* pneumonia.

Neutropenia is common after cyclophosphamide and may be used as a guide to dosing. WBC counts should be kept at >2,000/ μ L. Cell counts fall initially and then begin to rise about 7 to 10 days after dosing. Anemia and thrombocytopenia may be seen after cyclophosphamide therapy.^{356,359}

Lung fibrosis has been a consistent finding in animal studies of cyclophosphamide use.^{367,368} However, the frequency of this complication in humans has been difficult to define partly because of the presence of confounding variables, such as concomitant use of other cytotoxic drugs, opportunistic infections, diffuse pulmonary malignancy, radiation pneumonitis, and oxygen toxicity. Therefore, the literature is limited to case reports and small case series³⁶⁹ that suggest that drug withdrawal with or without corticosteroids

usually will resolve early manifestations of this side effect. A large prospective study using chest radiography in 192 patients receiving cyclophosphamide failed to find any case of lung fibrosis over 5 years.³⁶³

3.5.2.2 Pregnancy Classification—Cyclophosphamide is teratogenic during pregnancy (FDA category D), especially in the first trimester.³⁷⁰ Development of sterility variably occurs in both men and women during treatment with cyclophosphamide. The use of gonadotropin-releasing hormone prior to cyclophosphamide treatment may prevent primary ovarian failure in premenopausal women.³⁷¹ Other immunosuppressive agents, such as azathioprine, are believed to be safer during pregnancy.³⁷² Cyclophosphamide is associated with increased risk of inducing premature menopause.³⁷³

3.5.2.3 Monitoring—Reported monitoring for cyclophosphamide toxicity has usually included a CBC count, renal function studies, and urinalysis every 1 to 2 months while the patient is receiving therapy.³⁶¹ For those receiving intermittent IV therapy, CBC count is measured prior to the next dose, and urinalysis is performed every 1 to 2 months.³⁵⁹

Considerations for clinicians regarding cyclophosphamide for patients with lung disease and lung transplant recipients:

- *Monitoring blood work:* A CBC count and creatinine level should be obtained when commencing cyclophosphamide therapy and repeated at least every 4 to 6 weeks. Patients treated with intermittent IV dosing should have a CBC count prior to the next IV dosing. Urinalysis should be performed every 4 to 8 weeks to look for evidence of hemorrhagic cystitis. In patients with persistent, unexplained hematuria, cystoscopy should be strongly considered to evaluate for possible bladder cancer. Because cyclophosphamide can induce sterility in both men and women, counseling regarding ova and sperm harvesting prior to initiation of therapy should be considered. In women, gonadotropin-releasing hormone given prior to initiation of cyclophosphamide may prevent premature menopause.
- *Monitoring of drug clearance:* Cyclophosphamide is cleared by the kidneys, and direct toxicity to the bladder is the proposed mechanism for hemorrhagic cystitis and bladder cancer. Patients should be well hydrated on the day of dosing, with the recommendation of eight glasses of water as a rule of thumb. For patients at risk for bladder toxicity, coadministration of MESNA may reduce toxicity.
- *Monitoring for drug/drug interaction:* Cyclophosphamide will cause an increased rate of

bone marrow suppression when used with other cytotoxic drugs. An increased rate of neutropenia may also be seen when used with rituximab.

- *Prophylaxis against infections:* There are no special issues for cyclophosphamide. Prophylaxis recommendations are discussed in Table 12.

The following topics have been identified for prioritization for future research regarding cyclophosphamide:

- *The need for infection prophylaxis, especially for patients concurrently taking corticosteroids.*
- *The appropriate strategy for monitoring for infectious complications.*
- *Determination of the risk-benefit ratio of oral vs intermittent IV dosing.*

Information for patients:

- *Drink plenty of water on the day you take cyclophosphamide. A good goal is to drink eight glasses of water or its equivalent.*
- *Check your temperature frequently and report a fever to your physician immediately.*
- *Report to your physician signs of infection, such as cough, aches, fever, and chills; a wound or cut with redness, pain, discharge, or pus; pain; burning with urination; and nausea, vomiting, and diarrhea.*
- *Report shortness of breath or other changes in your breathing to your physician.*
- *Report any evidence of blood in your urine or pain when urinating to your physician.*

3.5.3 Leflunomide: The FDA approved leflunomide for use in rheumatoid arthritis in 1998. Three double-blinded, randomized, placebo-controlled trials of 1,865 patients demonstrated superiority over placebo but no consistent benefit compared with other disease-modifying antirheumatic agents.³⁷⁴⁻³⁷⁶ Subsequent results indicated that the treatment benefits and safety are durable for at least 2 to 5 years.^{377,378} In addition to rheumatoid arthritis, clinical trials of leflunomide as an antiinflammatory agent have been reported for Sjögren syndrome,³⁷⁹ systemic lupus erythematosus,³⁸⁰ and granulomatosis with polyangiitis.³⁸¹ Its use has also been described for sarcoidosis,³⁸² antisyntetase syndrome,³⁸³ relapsing polychondritis,³⁸⁴ adult-onset Still disease,³⁸⁵ and arthritis associated with systemic sclerosis.³⁸⁶ It has been used as an adjunctive medication for the prevention of acute and chronic rejection in solid organ transplant recipients.³⁸⁷ Besides its antiinflammatory properties, leflunomide antagonizes capsid assembly for CMV,³⁸⁸ and it has been used as second-line therapy for CMV and BK

Table 32—Monitoring of Leflunomide

Author/Year	Study Design	Disease	Comparator	Dose	No. Patients Treated	Duration of Therapy	Duration of Monitoring	Complications Noted ^a	Study Adequacy	Coadministered Agents	Comments
Emery et al ³⁷⁴ /2000	PRCT, DB, MC	RA	MTX	20 mg/d ^b	999	24 mo	2 y	Diarrhea, alopecia, nausea, rash, LFT elevations, HTN	4	NSAIDs Prednisone ≤10 mg/d	Two deaths in MTX group
Strand et al ³⁷⁵ /1999 and Cohen et al ³⁷⁷ /2001	PRCT, DB, MC	RA	Placebo MTX	20 mg/d ^b	508 in year 1 199 in year 2 extension	1-2 y	2 y	Diarrhea, HTN, LFT elevations, rash, abdominal pain	5	NSAIDs Prednisone ≤10 mg/d	None
Smolen et al ³⁷⁵ /1999, and Scott ³⁴⁷ /1977	PRCT, DB, MC	RA	Placebo Sulfasalazine	20 mg/d ^b	358	24 wk	24 wk, 2-y extension	Diarrhea, rash, nausea, alopecia	5	NSAIDs Prednisone ≤10 mg/d	None
Kalden et al ³⁷⁶ /2003	OL, MC	RA	OL extension of Smolen and Emery studies	20 mg/d ^b	214	2.5-5.8 y Mean, 4.8 y	Mean, 4.8 y	Diarrhea, HTN, LFT elevations, rash, eczema, URI	1	Not described	One death from sepsis possibly related
Baughman and Lower ³⁸² /2004	SC, RS	Pulmonary ± systemic sarcoidosis	Failed prior MTX monotherapy	10-20 mg/d ^b	32 (15 with MTX)	1-48 mo (median, 18 mo)	> 6 mo	Nausea	0	Prednisone ≤10 mg/d ^c	Successful when nausea limited MTX
Kalishvasser et al ³⁸² /2004	PRCT, DB, MC	Psoriasis	Placebo	20 mg/d ^b	186	24 wk	24 wk	Diarrhea, LFT elevation, fatigue	5	Topical	Neutropenia in one patient taking leflunomide
Poor and Strand ³⁸³ /2004	PRCT, DB, MC	RA	NA	20 vs 10 mg/d	402 1:1	24 wk	24 wk	Diarrhea, rash, anemia	4	Prednisone	None
Silverman et al ³⁸⁹ /2005	PRCT, DB, MC	JRA (pediatrics)	MTX	Weight based	47 per arm	16 wk 32-wk extension	48 wk	Headache, abdominal pain, alopecia, URI symptoms	5	Prednisone	One possible salmonellosis in leflunomide group
John et al ³⁹⁰ /2005	PS, OL, SC	CMV in renal transplant	None	10-40 mg/d ^{b,d}	17	3-12 mo	12 mo	One patient each with sepsis, pneumonitis, and psychosis	0	Immunosuppressives Ganciclovir	Complications unlikely related to leflunomide
Karamikolas et al ³⁹⁵ /2006	PRCT, OL	RA	CsA Leflunomide + CsA	20 mg/d	36 leflunomide 35 leflunomide + CsA	12 mo	12 mo	Alopecia, URI, rash, HTN, headache	2	Not described	More drop-outs in leflunomide group: One death

JRA = juvenile rheumatoid arthritis. See Table 5-7, 9, 12, and 27 legends for expansion of other abbreviations.

^aComplications that are more frequent in leflunomide group for controlled studies.^bFollowing loading dose (100 mg/d × 3 d).^cOne patient maintained on 40 mg/d.^dDose titrated to achieve therapeutic levels of the active metabolite, A77-1726.

virus infection in transplant recipients.^{389,390} Table 32 summarizes one study from the pulmonary literature³⁸² and nine studies in which leflunomide was used for nonpulmonary diseases.^{374-378,390-395} These studies provide information regarding toxicity of the drug.

3.5.3.1 Toxicity—The most common side effects reported in controlled trials are nausea, diarrhea, alopecia, hypertension, elevated liver enzymes, and rash. These side effects appear to be dose related and often resolve with reduction from 20 to 10 mg. In sarcoidosis, the occurrence of side effects (mainly nausea) during methotrexate treatment did not portend similar toxicity with leflunomide.³⁸² Postmarketing experience has demonstrated rare instances of serious infection, cytopenia, angioedema, fulminant hepatitis, interstitial pneumonitis, peripheral neuropathy, and severe dermatologic syndromes (Stevens-Johnson syndrome, erythema multiforme, toxic epidermal necrolysis). The postmarketing data are severely limited by ascertainment bias, concomitant immunosuppressive use, and presence of the underlying disease; therefore, attribution of these toxicities to leflunomide remains unclear.

Elimination of the active metabolite may be necessary when toxicity develops.³⁹⁶ Because of enterohepatic recirculation, use of cholestyramine 8 g tid is recommended.³⁹⁶ Charcoal is an acceptable alternative. Administration of three doses of cholestyramine to healthy volunteers resulted in reduction of plasma metabolite levels by 40% at 24 h and 49% to 65% at 48 h (FDA product document).³⁹⁶ A partial washout (three doses of cholestyramine) may be useful when side effects lead to the need for a dose reduction to 10 mg.³⁹⁶ Otherwise, new steady-state levels will not be reached for about 2 weeks. The drug and its metabolite are not removable with dialysis.³⁹⁶

Hepatic toxicity generally occurs within 6 months of initiating therapy. It is more common in patients with preexisting liver dysfunction or those using concomitant methotrexate.³⁹⁷ In clinical trials for rheumatoid arthritis, elevations of alanine aminotransferase (ALT) more than three times the upper limit of normal were observed in 2% to 4% of patients.³⁷⁴⁻³⁷⁶ These were almost always reversible with dose adjustment or discontinuation of the medication. The incidence of hepatocellular necrosis appears to be 100-fold less than for ALT elevations.³⁹⁸ A letter from the manufacturer in May 2001 detailed postmarketing reports of hepatotoxicity spanning worldwide experience with 104,000 patient-years of therapy.³⁹⁹ There were 296 cases of liver function abnormalities, including 15 of liver failure. Of these, 10 were deemed to be likely attributable to leflunomide use. When used in combination with methotrexate, elevation of liver tests occurred more frequently in the absence of folic acid supplementation.

Peripheral neuropathy has been reported in case series.⁴⁰⁰⁻⁴⁰² Analysis of 80 neuropathy cases reported to the FDA demonstrated a mean time to symptom onset of 6 months (range, 3 days-3 years); a better outcome was associated with stopping the drug within 30 days of symptom onset.⁴⁰¹ The neuropathy associated with leflunomide may be due to perineural vasculitis.⁴⁰⁰ A recent open-label, prospective, controlled study in 26 patients with rheumatoid arthritis demonstrated neuropathic symptoms in 54% vs 8% of patients treated with other agents.⁴⁰³ The symptoms usually did not correlate with neurophysiologic testing, but in one leflunomide-treated patient with abnormal nerve conduction studies, the symptoms resolved quickly after stopping the medication and cholestyramine washout. These data are somewhat difficult to interpret because of the background prevalence of neuropathic symptoms in rheumatoid arthritis.

Rare cases of Stevens-Johnson syndrome, toxic epidermal necrolysis, or erythema multiforme have occurred following the use of leflunomide.^{404,405} Lupus-like skin reactions have also been described.

Interstitial pneumonitis with leflunomide has been reported in case series, especially in Japan. These cases are confounded by potential ascertainment bias because the reporting system in Japan does not adequately distinguish infectious causes from drug toxicity. However, there are several other reports of likely lung toxicity due to the drug,^{406,407} usually manifesting as ground glass opacities, consolidation, or reticular infiltrates.⁴⁰⁸ Fatalities have occurred.

Whether preexisting lung disease from rheumatoid arthritis confers a higher risk of pneumonitis compared with methotrexate therapy is unclear. The largest data set to examine this issue, using a cohort of 62,734 patients treated with disease-modifying antirheumatic drugs, suggested that any increased incidence of pneumonitis in leflunomide-treated patients was likely a result of clinician preference (channeling bias) to treat patients with underlying ILD with leflunomide rather than methotrexate.⁴⁰⁹

Leflunomide increases renal excretion of uric acid and decreases tubular reabsorption of phosphate.⁴¹⁰ In clinical trials, this effect has not resulted in clinically significant hypophosphatemia. Use of live vaccines has not been studied in leflunomide.

3.5.3.2 Pregnancy Classification—There are no published data on the use of leflunomide in pregnant women.⁴¹¹ Leflunomide has been contraindicated in pregnancy (pregnancy category 10). Women of child-bearing age have been cautioned about effective birth control and receive pregnancy testing. Because of variability in individual metabolism, definitive elimination of the active metabolite is necessary prior to conception. The recommended protocol to achieve this is use of cholestyramine 8 g tid for 11 days followed

by testing to document plasma levels of <0.02 mg/L of the active metabolite.

3.5.3.3 Monitoring—Patients should have a CBC count, liver function panel, and phosphate and creatinine tests when commencing leflunomide therapy; these are repeated every 4 to 6 weeks for the first 6 months of treatment.^{377,391} If stable after 6 months, these parameters can be checked every 6 to 12 weeks.³⁸² Clinical monitoring for infections and signs of hepatotoxicity is also recommended. If leflunomide is coadministered with MTX, CBC count, liver function panel, and phosphate and creatinine levels should be obtained every 1 to 3 months indefinitely.^{377,382}

In some cases, investigators who encountered ALT elevations between twofold and threefold the upper limit of normal allowed a dose reduction to 10 mg/d with continued administration of leflunomide under close monitoring.³⁹¹ If elevations between twofold and threefold the upper limit of normal persisted despite dose reduction or if ALT elevations more than threefold the upper limit of normal were present, leflunomide was discontinued. In some cases, cholestyramine or charcoal were administered (with close monitoring, including retreatment with cholestyramine or charcoal as indicated).

Considerations for clinicians regarding leflunomide for patients with lung disease and lung transplant recipients:

- *Monitoring blood work:* A CBC count, liver function panel, and phosphate and creatinine levels should be obtained when commencing leflunomide therapy and repeated every 4 to 6 weeks for the first 6 months of treatment.^{377,391} If stable after 6 months, these parameters can be checked every 6 to 12 weeks.³⁸² Clinical monitoring for infections and signs of hepatotoxicity is also recommended. If leflunomide is coadministered with methotrexate, laboratory values should be obtained every 1 to 3 months indefinitely.^{377,382}
- *Monitoring of drug clearance:* Leflunomide is renally cleared, and dose modification should be considered for moderate to severe renal disease. The half-life of the drug is prolonged, and for patients with toxicity, cholestyramine should be used for rapid elimination.
- *Monitoring for drug/drug interaction:* Leflunomide will interact with methotrexate and trimethoprim/sulfamethoxazole. However the drugs can be given concurrently but may require more frequent monitoring of the CBC count. There are insufficient data for leflunomide, but based on published information regarding methotrexate, screening for the excessive use of alcohol or history of hepatitis C is recommended.

- *Prophylaxis against infections:* There are no special issues for leflunomide. Prophylaxis recommendations are discussed in Table 12.

The following topics have been identified for prioritization for future research regarding leflunomide:

- *The need for infection prophylaxis.*
- *The appropriate strategy for monitoring for infectious complications.*

Information for patients:

- *Check your temperature frequently and report a fever to your physician immediately.*
- *Report to your physician signs of infection, such as cough, aches, fever, and chills; a wound or cut with redness, pain, discharge, or pus; pain; burning with urination; and nausea, vomiting, and diarrhea.*
- *Report shortness of breath or other changes in your breathing to your physician.*
- *Report any neurologic symptoms (headache, dizziness, numbness, tingling, or weakness) to your physician.*

3.5.4 Methotrexate: Methotrexate is approved in the United States for use in rheumatoid arthritis, psoriasis, and several malignancies. In pulmonary diseases, it has been described most often for use either in sarcoidosis as a steroid-sparing agent⁴¹² or for disease unresponsive to corticosteroids.⁴¹³ The efficacy of methotrexate has also been reported for cutaneous,^{414,415} ocular,⁴¹⁶ musculoskeletal,⁴¹⁷ and neurologic sarcoidosis.^{354,418} Besides sarcoidosis, RCTs have suggested a role for methotrexate as a steroid-sparing agent in chronic asthma.^{419,420}

Positive effects in open-label trials have also been reported in granulomatosis with polyangiitis for induction of remission in non-life-threatening disease^{352,421} or for maintenance of remission after induction with cyclophosphamide.⁴²² There are also reports of beneficial effects for cryptogenic organizing pneumonia,⁴²³ polymyositis-dermatomyositis-associated ILD,⁴²⁴ Churg-Strauss syndrome,⁴²⁵ and steroid-resistant lung allograft rejection.⁴²⁶ Table 33 summarizes 15 RCTs^{352,412,419,420,422,427-436} and Table 34 summarizes 14 open-label trials in which methotrexate was studied for pulmonary diseases and where information regarding toxicity was presented.^{413,414,421,425,426,437-445}

3.5.4.1 Toxicity—Major toxicities from methotrexate include liver damage, pneumonitis, and cytopenias. Other common side effects include nausea, diarrhea, fatigue, rash, headaches, difficulty concentrating, and alopecia.⁴⁴⁶ Most large RCTs have monitored subjects for 1 to 2 years, leading to possible underestimates of

Table 33—Monitoring of Methotrexate (RCTs)

Author/Year	Study Design	Disease	Weekly Dose	Route	No. Patients Treated	Age, y	Duration of Therapy	Duration of Monitoring	Complications Noted	Study Adequacy	Comments	Malignancy/Pregnancy
Baughman et al ¹² /2000	DB, PRCT	Sarcoidosis	10 mg	Oral	MTX, 9; Placebo, 6	26-52	12 mo	12 mo	No different from placebo	1	None encountered	
Metzler et al ³⁶ /2007	DB, RCT	Granulomatosis with polyangiitis	15-20 mg	Oral	MTX, 28; Leflunomide, 26	25-67	21 mo	24 m	Nausea, 1; Infections, 12	1	None encountered	
De Groot et al ⁴² /1996	RCT	Granulomatosis with polyangiitis	0.3 mg/kg	IV	MTX, 22; T/S, 24; MTX + prednisone, 11; T/S + prednisone, 8	NA	Up to 3 y	Up to 3 y	Any side effects: MTX, 12; T/S, 6 Withdrawn: MTX, 2; T/S, 3	1	None encountered	
De Groot et al ³² /2005	RCT	ANCA-associated vasculitis	15-25 mg	Oral	MTX, 49; CYC, 46	22-78	12 mo	12 mo	Infection, 9; Leukopenia, 4; Hepatotoxicity, 7; Nausea, 1; Hypertension, 3; Allergy, 1; Infertility, 1; Transient nausea, 3; Rash, 1; Abnormal LFT, 5	1	Two deaths unrelated	
Mullarkey et al ¹⁹ /1988	DB, CO, PRCT	Asthma	15 mg	Oral	Both, 14	NA	6 mo	6 mo	Transient nausea, 3; Rash, 1	1	None encountered	
Shiner et al ⁴⁷ /1990	DB, PRCT	Asthma	15 mg	Oral	MTX, 38; Placebo, 31	NA	6 mo	6 mo	Abnormal LFT, 5	1	None encountered	
Dyer et al ⁴⁸ /1991	DB, CO, PRCT	Asthma	15 mg	Oral	Both, 10	NA	3 mo	6 mo	Anorexia; Alopecia; Stomatitis	1	None encountered	
Erzurum et al ⁴⁹ /1991	DB, PRCT	Asthma	15 mg	IM	19	NA	3 mo	12 mo	<i>Pneumocystis jirovecii</i> pneumonia, 1 (OL follow-up)	1	Death during OL follow-up of <i>P. jirovecii</i> pneumonia	
Taylor et al ⁴³⁰ /1993	DB, CO, PRCT	Asthma	15 mg	Oral	Both, 11	NA	11 mo	11 mo	Withdrawn due to adverse events, 2	1	None encountered	
Stewart et al ⁴³² /1994	DB, CO, PRCT	Asthma	15 mg	Oral	Both, 21	NA	7 mo	7 mo	Headache and nausea twice as frequent with MTX	1	None encountered	
Coffey et al ⁴³¹ /1994	DB, CO, PRCT	Asthma	15 mg	Oral	Both, 11	NA	3 mo	6 mo	No different from placebo	1	None encountered	
Ogitala et al ⁴³⁴ /1995	DB, PRCT	Asthma	15 mg	Oral	Triamcinolone, 6; MTX, 7; Neither, 6	NA	NA	NA	NA	1	NA	
Kanzow et al ⁴³³ /1995	DB, PRCT	Asthma	15 mg	Oral	24	NA	4 mo	4 mo	No different from placebo	1	None encountered	
Hedman et al ⁴³⁵ /1996	DB, CO, PRCT	Asthma	15 mg	Oral	Both, 12	NA	6 mo	6 mo	No serious side effects	1	None encountered	
Comet et al ⁴⁹ /2006	DB, PRCT	Asthma	10 mg	Oral	Both, 23	57.3 ± 12.3 y	12 mo	12 mo	Diarrhea, bronchospasm	1	None encountered	

CO = cross-over; T/S = trimethoprim/sulfamethoxazole. See Table 5, 7, 8, 12, and 29 legends for expansion of other abbreviations.

Table 34—Monitoring of Methotrexate (Non-RCTs)

Author/Year	Study Design	Disease	Weekly Dose	Route	No. Patients Treated	Age, y	Duration of Therapy	Duration of Monitoring	Complications Noted ^{a,b}	Study Adequacy	Comments Malignancy/Death Pregnancy
Lower and Baughman ^{41,3} /1990	OLT	Sarcoidosis	10 mg	Oral	14	NA	6-27 mo	6-27 mo	Pneumonia, 1	2	None encountered
Lower and Baughman ^{41,4} /1995	OLT	Sarcoidosis	10 mg	Oral	50	39 ± 9.1 ^a	>24 mo	>24 mo	Liver toxicity, 6 Cough, 1 Leukopenia, 1	2	None encountered
Gedalia et al ⁴¹ /1997	OLT	Sarcoidosis	10-15 mg/m ²	Oral	7	2-17	6 mo	6 mo	None	2	None encountered
Vucinic ⁴² /2002	OLT	Sarcoidosis	10-15 mg	Oral	91	33-70	>2 y	>2 y	None	3	None encountered
Metzler et al ⁴² /2004	OLT	Churg-Strauss syndrome	15-20 mg	Oral	36	NA	49 mo	48 mo	MTX pneumonitis, 1; infections; leukopenia	3	None encountered
Sneller et al ⁴³ /1995	OLT	Granulomatosis with polyangiitis	15 mg	Oral	42	NA	29 mo	29 mo	NR	4	NR
De Groot et al ⁴² /1998	OLT	Granulomatosis with polyangiitis	0.3 mg/kg	IV	17	NA	25 mo	25 mo	No significant side effects	4	None encountered
Langford et al ⁴² /1999	OLT	Granulomatosis with polyangiitis	15 mg	Oral	31	NA	13 mo	13 mo	Drug discontinuation, 2	4	None encountered
Reinhold-Keller et al ⁴³ /2002	OLT	Granulomatosis with polyangiitis	0.3 mg/kg	IV	71	NA	19 mo	19 mo	Leukopenia, 2	3	None encountered
Langford et al ⁴⁵ /2003	OLT	Granulomatosis with polyangiitis	15 mg	Oral	42	NA	32 mo	32 mo	Drug discontinuation, 2	4	None encountered
Mullarkey et al ⁴⁷ /1990	OLT	Asthma	15-50 mg	Oral	31	NA	>18 mo	>18 mo	AE, 15	3	None encountered
Shiner et al ⁴³ /1994	OLT	Asthma	15 mg	Oral	21	NA	15 mo	15 mo	Abnormal LFTs, 6 Discontinuation drug because of LFTs, 1 Nausea, 6 Resolution of nausea with IM administration, 5 Abnormal LFTs, 4 Discontinuation drug due to LFTs, 1 Infection, 1	3	None encountered
Yew et al ⁴⁰ /1996	OLT	Asthma	15 mg	Oral	9	NA	24 mo	24 mo	Abnormal LFTs, 4 Discontinuation drug due to LFTs, 1	3	None encountered
Cahill et al ⁴⁶ /1996	OLT	Lung transplant rejection	10-25 mg	Oral	12	NA	12 mo	12 mo	Cytopenia, 1 GI side effects, 2 Infections, 2	3	None encountered

See Table 5-8, 24, and 27 legends for expansion of abbreviations.

^aMay be the same patient population.^bToxicities measured by 5-point scale of the National Cancer Institute Common Toxicity Criteria, version 2 (http://www.eortc.be/services/doc/ctc/ctcv20_4-30-992.pdf).

a toxicity profile. In these studies, which include primarily rheumatoid arthritis and psoriasis populations, side effects led to drug discontinuation in ~30% of subjects. Adverse reactions during methotrexate therapy included transaminase elevation (21%), nausea (18%), and diarrhea (12%); one patient was withdrawn from the trial because of diarrhea.⁴⁴⁷ It appears that age > 60 years and impaired renal function are risk factors for toxicity.^{448,449} GI and hematopoietic effects are less than those encountered with azathioprine.⁴⁵⁰

Data from registries suggest that methotrexate is well tolerated in long-term use. In a British registry of 673 individuals prescribed methotrexate for rheumatologic diseases, side effects attributed to the drug led to discontinuation in 36.3%.⁴⁵¹ The most common reasons for discontinuing therapy were GI symptoms (10.8%), abnormal liver function tests (5.5%), cytopenias (5.5%), pulmonary symptoms (3%), and cutaneous abnormalities (2.1%). Life-threatening adverse events occurred in 1.7% of the cohort. In a single-center study of 26 patients treated with methotrexate and followed for 84 months (12 treated for all 84 months), Weinblatt et al⁴⁵² found that the drug was stopped in four patients as follows: three for toxicity (one alopecia, two pneumonitis) and one for noncompliance. This stable pattern held over a 10-year follow-up of these patients.⁴⁵³

Pulmonary toxicity is well described with methotrexate treatment.^{450,454,455} Pulmonary toxicities are not prevented by folic acid administration. Patterns of pulmonary toxicity may include pneumonitis, bronchitis with airways hyperreactivity, pulmonary fibrosis, bronchiolitis obliterans with organizing pneumonia, and diffuse alveolar damage. The most commonly reported manifestation is hypersensitivity pneumonitis. The incidence has been reported between 1% and 5%.⁴⁵⁶ Although most cases report an ILD, unexplained cough that recurred with rechallenge with methotrexate has been reported.⁴¹⁴ In some cases, these patients were treated with leflunomide without recurrence of cough.³⁸² Prolonged methotrexate treatment was not associated with chronic ILD, and routine high-resolution CT and serial pulmonary function tests were not useful in monitoring patients.⁴⁵⁷

Liver toxicity has also been reported with prolonged methotrexate treatment. One prospective study of patients with rheumatoid arthritis treated with methotrexate stopped drug administration because of hepatotoxicity in 5% of cases.⁴⁵¹ Severe hepatic toxicity is a less common, but more worrisome toxicity from the drug. One detailed study of a large group of patients with rheumatoid arthritis treated with methotrexate identified severe liver failure and cirrhosis in 24 patients, with a 5-year cumulative incidence of one per 1,000 patients. Roenigk et al⁴⁵⁸ developed a

histologic classification (grade 0-IV) commonly used to assess methotrexate toxicity. A meta-analysis of 636 patients with rheumatoid arthritis or psoriasis in 15 studies concluded that 28% of patients progressed at least one grade while on therapy. Five percent of the patients had advanced liver disease (grade IIIB or IV). The major risk factors for developing liver damage in that study included cumulative dose of methotrexate, heavy alcohol use, and underlying psoriasis.⁴⁵⁹ Patients had a 6.7% chance of progressive liver damage for each cumulative gram of methotrexate. These data have led to the recommendation that liver biopsy be considered after each 1 to 1.5 g of methotrexate.⁴⁵⁸ Unfortunately, four of these 24 patients died of the initial liver failure.⁴⁶⁰ In sarcoidosis, hepatotoxicity has been reported in up to 15% of cases.^{414,461} Routine liver function testing usually is performed every 4 to 12 weeks while receiving the drug, as recommended by other groups.^{462,463} Liver biopsy samples used to monitor for irreversible hepatotoxicity have been recommended by some⁴⁵⁸ but are no longer recommended by the American College of Rheumatology,⁴⁶² which instead recommends monitoring transaminase levels. Only if the transaminase levels are elevated in more than one-half of the testing in the prior year does the American College of Rheumatology recommend a biopsy.⁴⁶² However, adherence to only blood tests can still miss an occasional patient with advanced liver disease.⁴⁶⁴ In sarcoidosis, 100 liver biopsies were performed in 57 patients after each 1 to 1.5 g of accumulated doses. Fourteen patients had changes consistent with methotrexate toxicity (47 had changes due to sarcoidosis). There was no pattern of liver function tests, duration of therapy, or prior liver biopsy samples that predicted who would have methotrexate changes.⁴⁶¹ Increased alcohol consumption has led to increased methotrexate toxicity in some studies,⁴⁶⁵ but other studies have failed to determine a level of alcohol intake associated with an increased risk.^{466,467} Patients with hepatitis C are at increased risk for methotrexate hepatotoxicity.⁴⁶⁸

The duration of exposure to methotrexate likely accounts for a substantial proportion of its toxicity. Therefore, once-weekly regimens are favored and lead to fewer side effects. Delayed clearance of the medication because of renal insufficiency or the presence of third-space effusions^{469,470} or GI obstruction⁴⁷¹ leads to prolonged circulating methotrexate, increasing the risk of toxicity. The accumulation of methotrexate in ascites and pleural effusions can lead to prolonged exposure to the drug.

3.5.4.2 Folic Acid Supplementation—Using folic acid can minimize the risk for many of the side effects. Typical doses are 1 to 2 mg/d, although daily doses of up to 5 mg have been described. Because methotrexate is a dihydrofolate reductase inhibitor, folic

acid supplementation may bypass the methotrexate-induced blockade during nucleic acid synthesis. A well-designed RCT of folic acid supplementation vs placebo in patients with rheumatoid arthritis addressed the question of the effects of folic acid on side effects and efficacy of the medication.⁴⁷¹ In this report, use of folic acid 5 mg/d or 27.5 mg/wk had no effect on drug efficacy in these patients but significantly reduced toxicity scores for both doses. A second, larger study (n = 434) in patients with rheumatoid arthritis obtained similar results. Methotrexate-related toxicity led to discontinuation in 38% of placebo-treated patients vs 17% of those taking 1 to 2 mg/d folic acid.⁴⁷² There were also no differences in treatment effectiveness. It has been shown that low-dose methotrexate treatment in patients with rheumatoid arthritis leads to an increased plasma homocysteine level, a risk factor for cardiovascular disease. In a randomized trial, patients treated with methotrexate and concomitant folic or folinic acid had lower homocysteine levels than those treated with methotrexate and placebo.⁴⁷³ There was no correlation between homocysteine levels and either toxicity or therapeutic response.

3.5.4.3 Pregnancy Classification—Patients have been advised not to become pregnant or father a child while taking methotrexate.⁴⁷⁴ The drug can induce a medical abortion in >90% of patients after a single dose.⁴⁷⁵ The teratogenic effect is not clear, and normal pregnancies have occurred when methotrexate therapy was discontinued during the first trimester.⁴⁷⁶ The drug is not recommended during breast-feeding.^{474,477} The effect of methotrexate on the ovaries is short lived, and the drug seems to have no effect beyond 6 months.

3.5.4.4 Monitoring—Patients taking methotrexate have undergone routine CBC counts and assessment of renal function.^{478,479} For patients with leukopenia, the dose has been adjusted based on the WBC count.¹³ In one study, 26% of patients had one or more hematologic abnormalities. More than 95% of these patients had symptoms consistent with viral infection, and the abnormality resolved within 1 month of withholding the drug and did not recur with rechallenge.⁴⁸⁰ Liver function tests, especially of the transaminases, are monitored.^{462,478} The routine use of liver biopsy after every cumulative dose of 1 to 2 g methotrexate is controversial. Patients have been asked about nausea, diarrhea, and stomatitis. If present, these conditions have responded to dose reduction and the addition or an increase in dosage of 1 mg folic acid.⁴⁷¹

Considerations for clinicians regarding methotrexate for patients with lung disease and ung transplant recipients:

- **Monitoring blood work:** Patients should be monitored with a CBC count, liver function panel, and phosphate and creatinine levels when commencing methotrexate therapy, and the tests should be repeated every 4 to 12 weeks. Clinical monitoring for infections and signs of hepatotoxicity is also recommended. Patients with baseline transaminases or bilirubin levels of more than three times the upper limit of normal probably should not receive the drug.
- **Monitoring of drug clearance:** Methotrexate is cleared by the kidney, and the dose may require modification even with mild renal impairment. Patients with moderate to severe renal impairment (glomerular filtration rate <30 mL/min) normally should not be treated with methotrexate. Folic acid supplementation of 1 mg/d has been used.
- **Monitoring for drug/drug interaction:** Methotrexate will interact with leflunomide and trimethoprim/sulfamethoxazole; however, the drugs can be given concurrently but may require more frequent monitoring of the CBC count. Screening for the excessive use of alcohol or history of hepatitis C is recommended.
- **Prophylaxis against infections:** There are no special issues for methotrexate. Prophylaxis recommendations are discussed in Table 12.

The following topics have been identified for prioritization for future research regarding methotrexate:

- *The need for infection prophylaxis.*
- *The appropriate strategy for monitoring for infectious complications.*
- *The need for liver biopsy after a cumulative dose of 1 to 2 g.*
- *Comparison of subcutaneous vs oral administration in terms of efficacy and safety.*

Information for patients:

- *Check your temperature frequently and report a fever to your physician immediately.*
- *Report to your physician signs of infection, such as cough, aches, fever, and chills; a wound or cut with redness, pain, discharge, or pus; pain; burning with urination; and nausea, vomiting, and diarrhea.*
- *Report shortness of breath or other changes in your breathing to your physician.*

3.5.5 Mycophenolic Acid Derivatives: Mycophenolate mofetil, the morpholinoethyl ester prodrug of

Table 35—Monitoring of Mycophenolate

Author/Year	Study Design	Disease	Dose ^a	No. Patients Treated	Age, y	Duration of Therapy	Duration of Monitoring	Monitoring Used	Complications Noted	Study Adequacy	Coadministered Agents	Comments
Palmer et al ¹² /2001	PRCT, OL, MC	Lung transplant	1 g bid	43	≥18	6 mo	6 mo	Clinical evaluation; bronchoscopy	Leukopenia GI symptoms	3	CNI, corticosteroid	Drug continued more frequently for low WBC count and GI symptoms than for AZA arm
EMMCSG ⁹⁶ /1995	PRCT, OL, MC	Renal transplant	1 g bid (n = 165) 1.5 g bid (n = 160)	325	≥18	6 mo	6 mo	Clinical evaluation; renal biopsy	GI AEs, leukopenia, and anemia more common vs placebo group	5	CNI, corticosteroid	3 g daily dose tolerated less well than 2 g daily dose
Sollinger ⁹⁷ /1995	PRCT, DB, PC, MC	Renal transplant	MMF group 1, 1 g bid MMF group 2, 1.5 g bid	Group I, 167 Group II, 166	≥18	≥6 mo	≥6 mo	Clinical evaluation; renal biopsy	GI AEs (diarrhea, esophagitis, gastritis, hemorrhage) Neutropenia	5	CNI, corticosteroid, ATG	More GI events and neutropenia in MMF groups compared with AZA group (n = 166)
Eisen et al ¹⁰ /2005	PRCT, DB, PC, MC	Heart transplant	1 g bid	MMF, 289 AZA, 289	Mean, 52.1	3 y	3 y	Clinical evaluation; cardiac function; endomyocardial biopsy	Esophagitis and diarrhea more common for MMF vs AZA	5	CsA, corticosteroid ± OKT3 induction therapy	CMV tissue invasion and <i>Herpes simplex</i> infection more frequent in MMF patients with OKT3 induction therapy
Kobashigawa et al ⁹⁸ /2006	PTCT, SB, MC	Heart transplant	MMF, 1.5 mg bid MPS, 1,080 mg bid	MMF, 76 MPS, 78	≥18	12 mo	12 mo	Clinical evaluation; endomyocardial biopsy	Leukopenia (MPS, 19.5%; MMF, 17.6%); diarrhea (MPS, 12.8%; MMF, 22.4%)	4	CsA, corticosteroid ± induction therapy	GI AEs required study discontinuation in only two subjects (MPS group) (Continued)

Table 35—Continued

Author/Year	Study Design	Disease	Dose ^a	No. Patients Treated	Age, y	Duration of Therapy	Duration of Monitoring	Monitoring Used	Complications Noted	Study Adequacy	Coadministered Agents	Comments
Groetzner et al ⁴⁵⁶ /2006	PS, OL, SS	BO in lung transplant recipients	Target trough MPA level, 2–4 ng/mL first 12 mo posttransplant year, 1.5–4 ng/mL $\geq$ 12 mo posttransplant	12	37 $\pm$ 14	14.8 $\pm$ 1.4 mo	14.8 $\pm$ 1.4 mo	Clinical evaluation, PFT, bronchoscopy, serum Cr level	Leukopenia, anemia, thrombocytopenia, GI AEs (associated with elevated MPA trough levels)	1	CNI, sirolimus, corticosteroid	Patients taking CNI, MMF, and corticosteroid were converted to sirolimus (sirolimus added and CNI dose decreased) Serum Cr level improved MPA levels lower in patients taking CsA compared with those taking tacrolimus (especially those with CF) MMF given to replace AZAGFR increased
Gerbase et al ⁴⁵⁷ /2003	OS, SS	Lung transplant	25–35 mg/kg/dmax, 2 g/d	30	46 $\pm$ 11	$\geq$ 2 y	$\geq$ 2 y	Clinical evaluation	All AEs attributed to CNI therapy	1	CNI, corticosteroid	MPA levels lower in patients taking CsA compared with those taking tacrolimus (especially those with CF) MMF given to replace AZAGFR increased
Soccal et al ⁴⁵⁸ /1999	OS, SS	Lung transplant	1 g bid	14	Not stated	$\geq$ 6 mo	$\geq$ 6 mo	Serum Cr level	Not stated	1	CNI, corticosteroid	MPA levels lower in patients taking CsA compared with those taking tacrolimus (especially those with CF) MMF given to replace AZAGFR increased
Zuckermann et al ⁴⁵⁹ /1999	OS, SS	Lung transplant	500 mg bid	22	13–67	Median, 19 mo	Median, 19 mo	Clinical evaluation, serum Cr level	GI symptoms, 8 Leukopenia, 1	1	CNI, corticosteroid	AZA replaced by MMF Improved CrCl
O'Hair et al ⁴⁶⁰ /1998	OS, SS	Lung transplant	1 g bid	22	$\geq$ 18	$\geq$ 7 mo	$\geq$ 7 mo	Clinical evaluation, bronchoscopy, PFT	Abdominal pain, 31% Diarrhea, 17% Leukopenia, 11%	2	CNI, corticosteroid	GI AEs subsided with cessation of MMF, and all patients tolerated gradual reintroduction of MMF
Swignis et al ⁴⁶¹ /2006	RS, SS	CTD-related ILD	1 g bid	28	49–66	36 patient-y	187–632 d	Clinical evaluation, PFT	Diarrhea, 2 Hiccups, 1 Leukopenia, 1 Oral ulcer, 1 Recurrent pneumonia, 1	3	Corticosteroid	Lack of systematic data collection

CTD = connective tissue disease; EMMCSG = European Mycophenolate Mofetil Cooperative Study Group; MPS = mycophenolate sodium. See Table 5, 6, 8–13, 18, 24, and 28 legends for expansion of other abbreviations.

^aAll studies used MMF.^{452–465}

mycophenolic acid (MPA), has regulatory approval for the prophylaxis of organ rejection in cardiac, liver, and renal transplantation in combination with cyclosporine and corticosteroids.⁴⁸¹ Mycophenolate has been administered for prophylactic treatment of lung transplant recipients.^{312,482-485} It has also been administered for the treatment of bronchiolitis obliterans in lung transplant recipients,⁴⁸⁶ scleritis,⁴⁸⁷ uveitis,⁴⁸⁸ lupus nephritis,⁴⁸⁹ retroperitoneal fibrosis,⁴⁹⁰ rheumatoid arthritis,⁴⁹¹ granulomatosis with polyangiitis,⁴⁹² sarcoidosis,⁴⁹³ systemic lupus erythematosus,⁴⁹⁴ and pulmonary disease associated with various collagen vascular disorders.⁴⁹⁵ Table 35 summarizes 11 trials in which mycophenolate was administered to patients for various conditions and provides important information regarding toxicity.^{310,312,482-486,495-498} This table includes seven studies in which the drug was given for pulmonary diseases.^{312,482-486,495}

3.5.5.1 Toxicity—The elimination half-life of immediate-release MPA is 16 to 18 h,^{481,499} and that of delayed-release MPA is 8 to 16 h.⁵⁰⁰ Mycophenolate is extensively converted to MPA glucuronide, which is extensively cleared through renal excretion.⁴⁸¹ Adverse reactions associated with MPA administration include cardiovascular effects (systemic hypertension, peripheral edema, tachycardia),^{500,501} dermatologic effects (rash, skin neoplasm),⁵⁰¹ endocrinologic effects (hyperglycemia, cushingoid change, hirsutism),^{500,501} metabolic effects (hypercholesterolemia, hypophosphatemia, hypokalemia, hyperkalemia),^{500,501} GI effects (nausea, anorexia, vomiting, dyspepsia, abdominal pain, diarrhea, constipation),^{481,491,497,500,502,503} hematologic effects (anemia, RBC aplasia, leukopenia, thrombocytopenia, leukocytosis),^{481,500,501,503-505} opportunistic infection,^{481,501,506,507} musculoskeletal effects (bone pain, leg cramps, myalgias, hand cramps),⁵⁰⁸ neurologic effects (headache, tremor, insomnia, dizziness, anxiety),^{491,500,501,506} ocular changes (blurred vision, cataracts, blepharitis, keratitis, glaucoma, macular abnormalities),^{500,506} genitourinary effects (infection, hematuria, tubular necrosis, urinary frequency, burning on urination, kidney stones, vaginal burning, vaginal bleeding),^{500,501} and respiratory effects (increased cough, dyspnea, infection, pneumonitis, fibrosis).^{481,500,501} There are insufficient data to determine whether lymphoma or nonlymphomatous malignancies are increased as a result of using mycophenolate. A number of cases of progressive multifocal leukoencephalopathy have recently been observed in patients receiving therapy (FDA alert).

Several drug interactions can occur with mycophenolate. Activated charcoal, aluminum or magnesium salts, cholestyramine, colestevlam, colestipol, or iron can inhibit absorption from the GI tract.^{509,510} Coadministration of mycophenolate and azathioprine may cause increased inhibition of purine metabolism.

Mycophenolate can increase plasma concentration of acyclovir or ganciclovir, especially when renal impairment is present.^{40,501} Mycophenolate may decrease exposure to hormonal therapies.^{40,481} Patients receiving mycophenolate may have an inadequate immunologic response to vaccination.⁴⁰

3.5.5.2 Pregnancy Classification—Mycophenolate may have teratogenic or embryocidal effects on the fetus,⁵⁰⁰ and patients receiving immunosuppressive drugs, including mycophenolate, have been advised to avoid pregnancy. It has been suggested that mycophenolate only be used in pregnant women if the potential benefit justifies the potential risk to the fetus (FDA class D),⁵⁰⁰ but it should be noted that the FDA has recently issued a black box warning for use of MPA derivatives during pregnancy.

3.5.5.3 Monitoring—Studies regarding the clinical use of MPA report obtaining weekly CBC counts for the first month of treatment, twice monthly for the second and third months, and once a month for the remainder of the first year. Plasma levels of MPA have been used to guide therapy as well as to detect toxicity.^{511,512}

Considerations for clinicians regarding MPA derivatives for patients with lung disease and lung transplant recipients:

- *Monitoring blood work:* CBC counts should be monitored every 1 to 3 months as long as patients are on therapy.
- *Monitoring of drug clearance:* Mycophenolate blood levels may be obtained if signs and symptoms of GI intolerance develop (eg, diarrhea). High blood levels suggest that mycophenolate may be a cause of diarrhea.
- *Monitoring for drug/drug interaction:* Live vaccines should be avoided while patients are being treated with mycophenolate. Concomitant use of azathioprine should be avoided.
- *Prophylaxis against infections:* No specific recommendations are available.

The following topics have been identified for prioritization for future research regarding MPA derivatives:

- *The need for infection prophylaxis.*
- *The risk of neurologic complications (eg, progressive multifocal leukoencephalopathy).*
- *The risk of malignancy.*
- *The appropriate strategy for monitoring for infectious complications.*

Information for patients:

- *Check your temperature frequently and report a fever to your physician immediately.*

- Report to your physician signs of infection, such as cough, aches, fever, and chills; a wound or cut with redness, pain, discharge, or pus; pain; burning with urination; and nausea, vomiting, and diarrhea.
- Report shortness of breath or other changes in your breathing to your physician.
- Report any neurologic symptoms (headache, dizziness, numbness, tingling, or weakness) to your physician.

Recommendations for the monitoring of cytotoxic agents for patients with lung disease and lung transplant recipients:

3.5a. For patients who will undergo concurrent therapy with azathioprine and allopurinol, a reduction in dose of azathioprine is recommended (Grade 1A).

3.5b. For patients who undergo azathioprine therapy, obtaining CBC counts and renal/hepatic profiles every 1 to 3 months is recommended (Grade 1B).

3.5c. For patients who will undergo cyclophosphamide therapy, monitoring of CBC count, renal profile, and urinalysis at least monthly for dose adjustment is recommended (Grade 1B).

3.5d. For patients who will undergo cyclophosphamide therapy, increased fluid intake (eg, 2 L in addition to normal intake in adults; additional volume given to children needs to be calculated on the basis of body weight) on the days of therapy is recommended (Grade 1C).

3.5e. For patients who undergo or have undergone cyclophosphamide therapy and develop hematuria, further evaluation is recommended (Grade 1B).

3.5f. For patients who will undergo leflunomide or methotrexate therapy, screening for the use of alcohol and chronic viral hepatitis prior to treatment is recommended (Grade 2C).

3.5g. For patients who undergo methotrexate or leflunomide therapy, performance of liver function tests and CBC counts is recommended (Grade 1C).

3.5h. For patients who undergo methotrexate therapy, folic acid supplementation is recommended (Grade 1A).

3.5i. For patients who undergo leflunomide therapy and develop neuropathic symptoms, prompt

consideration of discontinuing therapy and washing out with cholestyramine is recommended (Grade 1C).

3.5j. For patients who undergo methotrexate (Grade 1B) or leflunomide (Grade 1C) therapy and develop new or worsening signs or symptoms of lung disease, further evaluation is recommended.

3.5k. For patients who undergo methotrexate therapy and develop persistently elevated liver transaminases above their own baseline, cessation of treatment or evaluation by liver biopsy is recommended (Grade 1B).

3.5l. For patients with renal insufficiency, ascites, or pleural effusions who undergo methotrexate therapy, decreased methotrexate clearance may be present, and dose reduction may be required (Grade 2C).

3.5m. For patients who undergo mycophenolic acid therapy and develop adverse GI effects, including diarrhea, interruption of therapy or reduction in dose is recommended (Grade 1B).

3.5n. For patients who undergo mycophenolic acid therapy and develop signs or symptoms of progressive multifocal leukoencephalopathy, cessation of treatment is suggested (Grade 2C).

3.6 Mammalian Target of Rapamycin Inhibitors

3.6.1 Everolimus: Everolimus was developed for the prevention of acute and chronic rejection after solid organ transplantation.⁵¹³ Everolimus is not approved by the FDA for lung transplantation.⁵¹³ Everolimus is a derivative of sirolimus; it was synthesized to have an enhanced bioavailability compared with that reported for sirolimus.^{514,515} Everolimus inhibits both the immune and the nonimmune response to the allograft.^{514,515} Evidence suggests that when used in combination with cyclosporine and corticosteroids that everolimus may be able to suppress the fibroproliferative processes and attenuate bronchiolitis obliterans in human lung transplant recipients. Table 36 summarizes the two studies in which everolimus administration was studied in lung transplant patients.^{316,516}

3.6.1.1 Toxicity—Leukopenia, thrombocytopenia, and anemia occur commonly with everolimus. Other common adverse effects include hypercholesterolemia, hyperlipidemia, hypertriglyceridemia, and hypertension. Pneumonia and other infections can occur more frequently.

Table 36—Monitoring of Everolimus

Author/Year	Study Design	Disease	Dose	No. Patients Treated	Age, y	Duration of Therapy	Duration of Monitoring	Monitoring Used	Complications Noted	Study Adequacy	Comments Malignancy/Death Pregnancy
Snell et al ³¹⁶ /2006	MC, PS, randomized, DB, ITT everolimus vs AZA	Stable lung or heart transplant 3-36 mo posttransplant	3 mg/d (1.5 mg bid)	Everolimus, 101 AZA, 112	46 ± 13	24 mo	24 mo	Levels obtained only for research, not for clinical information (6.6 ng/mL; 2.8-11.8 ng/mL)	Serious infections, 40.5% Bacteria, 35.1% Fungal, 27.9% Pneumonia, 11.7% Leukopenia, 23.4% (NS) Hyperlipidemia, 19.8% Hypercholesterolemia, 14.4% Anemia, 13.5% Thrombocytopenia, 12.6% Increased Cr level in 71% vs 41%	5	Skin malignancy and PTLD observed in eight patients the first year and five the second year, with no difference with the AZA arm Low PTLD incidence No increase in viral infections
Doyle et al ³¹⁶ /2001	Phase I, MC, randomized DB, two-treatment, two-period, two-sequence CO No placebo arm	Stable lung transplant patients 3 mo posttransplant, in CsA, steroids, and AZA	Sequence I: 0.1 mg/kg (max, 7.5 mg) followed by 0.035 mg/kg, (max, 2.5) Sequence II: Started with the low and continued with the high dose Usual dose for the CF was 7.8 ± 4.1 mg/kg/d for non-CF and 4.4 ± 1.7 mg/kg/d	20 (8 with CF and pancreatic insufficiency)	CF group, 32.4 ± 8.8 Non-CF group, 49.9 ± 11.7	1 wk in the higher-dose arm, 1 wk off, and then 1 wk in the lower-dose arm Total duration of therapy 2 non-consecutive wks	2 wk	Whole blood levels for PD studies C _{max} , 10-12 ng/mL Decrease platelet count in 25% of high dose vs 10% Decrease > 50,000 in 7 of 20 (35%) Decreased lymphocytes, high dose 20% vs low dose 5.6% Only one patient with significant leukopenia Mean total cholesterol did not change significantly with either dose Mild increase of triglyceride levels; 20% had a significant increase > 455	Headache, 20% Tachycardia, 15% HTN, 10% Edema, 10% Decrease platelet count in 25% of high dose vs 10% Decrease > 50,000 in 7 of 20 (35%) Decreased lymphocytes, high dose 20% vs low dose 5.6% Only one patient with significant leukopenia Mean total cholesterol did not change significantly with either dose Mild increase of triglyceride levels; 20% had a significant increase > 455	3	No deaths or withdrawals because of the study medication

ITT = intention to treat; PD = pharmacodynamics. See Table 5, 7, 9-11, 15, and 33 legends for expansion of other abbreviations.

There is very limited experience with everolimus in lung transplantation, and no studies have compared it with a placebo. Everolimus was compared with azathioprine in a multicenter, prospective, randomized, double-blind, intention-to-treat study and was found to be associated with a significant increase in serious infections (40.5% vs 22.5%, $P = .006$), pneumonia (11.7% vs 1.8%, $P = .006$), hyperlipidemia (19.8% vs 4.5%, $P = .001$), hypercholesterolemia (14.4% vs 4.5%, $P = .02$), anemia (13.5% vs 3.6%, $P = .003$), bacterial infections (35.1% vs 17.1%, $P = .004$), and fungal infections (27.9% vs 14.4%, $P = .021$), and no difference was found for *P. jirovecii* pneumonia, viral, and CMV infections.^{264,513}

The mechanisms by which everolimus exerts its effects are similar to those for sirolimus. However, there is no experience with the medication in the immediate posttransplant period; therefore, the risk for anastomotic dehiscence is not known.

3.6.1.2 Pregnancy Classification—No studies of teratogenicity in animals have been published, and no epidemiologic studies have been published regarding everolimus treatment during pregnancy in humans.

3.6.1.3 Monitoring—Few data are available on monitoring everolimus blood levels. Clinical trials with everolimus have monitored whole-blood trough levels with target concentrations of at least 3.0 ng/dL.⁵¹³ Monitoring of lipid profile, CBC with differential, liver function, glucose level, and routine blood chemistry levels may be useful during therapy to avoid toxicity.⁵¹³

Considerations for clinicians regarding everolimus for patients with lung disease and lung transplant recipients:

- **Monitoring blood work:** In addition to monitoring everolimus levels regularly, CBC count, renal function, and lipid profile should be monitored closely.
- **Monitoring of drug clearance:** Everolimus is metabolized through the hepatic mixed-function oxidase system (CYP3A4) and excreted through the liver, although both the kidney and the gut may contribute to its elimination. Various medications are known to either increase or decrease everolimus concentrations by either inhibiting or inducing the CYP3A4 system.
- **Monitoring for drug/drug interactions:** Because everolimus is metabolized through the CYP3A4 system, drugs that affect this system will affect clearance of everolimus. A list of the medications that either induce or inhibit the CYP3A4 system are listed in Table 11. In addition, everolimus is

an inhibitor of CYP3A4 and may reduce the clearance of several medications, including digoxin, colchicine, and the HMG-CoA reductase inhibitors.

- **Prophylaxis against infections:** Prophylaxis against *P. jirovecii* should be implemented with the use of everolimus. Prophylaxis recommendations are discussed in Table 12.

Areas for future research regarding everolimus:

The following topics have been identified for prioritization for future research:

- *The optimal approach to monitoring blood levels of everolimus.*
- *The frequency of monitoring blood work and everolimus levels.*

Information for patients:

- *Adverse events associated with everolimus include anemia, high BP, increased cholesterol and triglyceride levels, liver problems, nausea, vomiting, diarrhea, abdominal pain, headache, and dizziness.*

3.6.2 Sirolimus: Sirolimus has regulatory approval for prophylaxis of organ rejection in patients aged ≥ 13 years receiving renal transplants.⁵¹⁷ There is interest for the use of sirolimus and its analogs for a number of clinical indications. These include immune modulation for clinical transplantation of solid organs, graft-vs-host disease, autoimmune diseases, autoimmune lymphoproliferative syndrome, and asthma. Sirolimus binds to FK-binding protein, and this complex binds to mammalian target of rapamycin (mTOR). This inhibits IL-2-mediated transduction pathways that promote T-cell proliferation. By blocking this stimulation, T-cell proliferation is arrested in the mid to late G_1 phase of the cell cycle.⁵¹⁸ Its antiproliferative and antiangiogenic effects are potentially useful in the treatment of cancer and attenuation of radiation-induced effects. The antiproliferative effects of sirolimus have also led to its successful use in cardiac stents to prevent restenosis.⁵¹⁹ Similarly, these antiproliferative properties may affect hypertrophic myocarditis, pulmonary fibrosis, hepatic fibrosis, and autosomal-dominant polycystic kidney disease. Tuberous sclerosis or lymphangioleiomyomatosis (LAM), PTEN (Cowden disease), LKB1 (Peutz-Jeghers syndrome), and NF1 (neurofibromatosis) have all been linked to the mTOR pathway, implicating a potential role for sirolimus and its analogs. Even diabetes mellitus and obesity are linked to the mTOR pathway, suggesting potential future uses for sirolimus and its analogs.⁵²⁰

Table 37—Monitoring of Sirolimus

Author/Year	Study Design	Disease	Dose	Route	No. Patients Treated	Age, y	Duration of Therapy	Duration of Monitoring	Complications Noted	Study Adequacy	Comments
MacDonald ⁵²⁵ /2001	PRCT, DB, MC	Renal transplant	2 mg/d, 5 mg/d, or placebo	Oral	227, 219, 130	15-71 (mean, 45)	1 y	1 y	Hyperlipidemia, hypercholesterolemia, arthralgias, anemia, thrombocytopenia, epistaxis, no difference infection except increased HSV	4	All patients received concomitant CsA HSV was not defined by culture but noted by ulcer on mucosal examination
Kahan ⁵²⁵ /2000	PRCT, DB, MC	Renal transplant	2 mg/d, 5 mg/d, or AZA	Oral	284, 274, 161	Mean, 45	1 y	1 y	Hyperlipidemia, hypercholesterolemia, anemia, thrombocytopenia, lymphocele, diarrhea, epistaxis	4	Sirolimus vs AZA, no placebo group All patients received concomitant CsA
Bissler et al ⁵²³ /2008	PS, OL	Tuberous sclerosis and LAM	Initial 0.25 mg/m ² daily followed by goal level 5-15 ng/mL	Oral	25, 25	NR	2 y	2 y	Hyperlipidemia, 52% Aphthous ulcer, 68% Infection, 68%	1	None or NR

LAM = lymphangioleiomyomatosis. See Table 5, 6, 9, 11, and 24 legends for expansion of other abbreviations.

Sirolimus has been shown to be effective in treating pulmonary complications of LAM, including chylothorax.^{519,521,522} This trial is in follow-up of a previously published consecutive series of patients treated with sirolimus for angiomyolipoma in tuberous sclerosis or LAM, which suggested an improvement in pulmonary function with treatment.⁵²³ In addition, information regarding the use of sirolimus in combination with tacrolimus and prednisone in lung transplant recipients was recently submitted in abstract form to the International Society for Heart & Lung Transplantation.⁵²⁴ Table 37 summarizes three studies with information regarding toxicity of sirolimus,^{523,525,526} including one that specifically examined patients with LAM.⁵²³

3.6.2.1 Toxicity—Sirolimus use is associated with hypertension and peripheral edema. These adverse effects are from trials where sirolimus was used in combination with cyclosporine. Other studies that have used cyclosporine-sparing regimens (with higher doses of sirolimus) appear to have lower incidence of these adverse effects.⁵¹⁷ Similarly, elevations in serum creatinine level were seen when used in combination with cyclosporine. The incidence of this adverse reaction was significantly lower in a series of patients using sirolimus alone.⁵¹⁷

Patients experienced diarrhea, dyspepsia, nausea, vomiting, and constipation during clinical trials. Renal transplants had a significantly higher incidence of ileus and rectal disorder in later trials using a higher sirolimus dose and subsequent cyclosporine withdrawal.⁵¹⁷

Sirolimus has multiple hematologic effects, including anemia and thrombocytopenia.^{525,526} Leukopenia also occurs and does not appear to be dose related.⁵²⁷

Hyperlipidemia and hypercholesterolemia are dose-related effects of sirolimus.^{523,524,526,528,529} Patients receiving sirolimus have been monitored for development of these effects.

Infectious disease complications associated with the use of sirolimus are difficult to interpret given the concomitant immunosuppressive agents used in the clinical trials. The overall rate of infections did not appear to increase with the addition of sirolimus to the immunosuppression regimen in renal transplant recipients except for an increased risk of herpes simplex mucosal ulcerations.⁵²⁶ This finding appears to be corroborated by the finding of aphthous ulcers during a trial evaluating the use of sirolimus alone in patients with tuberous sclerosis or LAM.⁵²³

Significant pulmonary complications warrant further mention given the potential use in diffuse parenchymal lung disease. There are many case reports of the development of diffuse parenchymal lung disease in several different populations. These include renal transplant,⁵³⁰⁻⁵³⁵ liver transplant,⁵³⁶⁻⁵⁴⁰ and heart

transplant.^{500,541-544} Although data outlining the extent of the risk are scant, product information indicates a higher rate of DVT and pulmonary embolism.⁵¹⁷

Surgical wound healing can be affected by the use of this agent. In particular, de novo use of sirolimus in the lung transplant population resulted in significantly higher rates of bronchial wound dehiscence in two series.^{545,546} Wound-healing complications have also been noted in the renal and liver transplantation literature. The prevalence of this complication appears to be related to patient factors as well as to the dosing regimen.^{528,547,548}

3.6.2.2 Drug Interactions—Sirolimus is a known substrate for both CYP3A4 and P-glycoprotein, thus coadministration of sirolimus with agents known to be strong inhibitors (ketoconazole, voriconazole, itraconazole, erythromycin, telithromycin, or clarithromycin) or strong inducers of CYP3A4 or P-glycoprotein (rifampin) have not been recommended for use with sirolimus.⁵¹⁷

3.6.2.3 Pediatrics—Safety and efficacy in pediatric patients aged < 13 years or in pediatric renal transplant recipients have not been established.⁵¹⁷

3.6.2.4 Pregnancy Classification—Although not mutagenic, teratogenic, or carcinogenic in animals, prematurity, fetal mortality, reduced fetal weight, and fetal hypertrophy have been reported.⁵⁴⁹ Current guidelines recommend against the use of sirolimus during human pregnancy.⁵⁵⁰ The manufacturer recommends that women of childbearing potential use effective contraception prior to beginning sirolimus therapy, during treatment, and for at least 12 weeks after treatment has been stopped.⁵¹⁷

3.6.2.5 Monitoring—Prior to initiation, patients underwent routine hematologic and metabolic testing in clinical trials with sirolimus.^{523,525,526} Although trials used different exclusion criteria, a fasting serum triglyceride level > 500 mg/dL appears to be a contraindication to initiation of therapy. Similarly, a WBC count < 4 × 10⁹/L or a platelet count < 100 × 10⁹/L should be viewed with caution prior to initiating therapy. Based on the adverse effects listed previously, clinical trials did perform routine metabolic, hematologic, renal, and hepatic follow-up. The protocols varied in the intensity of this follow-up, with increased monitoring upon initiation of the protocol. Routine drug level monitoring has not been recommended, except in pediatric patients, in patients with hepatic impairment, and during concurrent administration of CYP3A4 and P-glycoprotein inducers and inhibitors and if cyclosporine dose is markedly changed or discontinued.⁵¹⁷ There is no formal recommendation regarding appropriate drug level; however, clinical trials generally had average drug levels that ranged from 5 to 15 ng/mL (as measured by whole-blood chromatographic assays).^{517,551}

Considerations for clinicians regarding sirolimus for patients with lung disease and lung transplant recipients:

- *Monitoring blood work:* In addition to monitoring sirolimus levels regularly, CBC count, renal function, and lipid profile should be monitored closely.
- *Monitoring of drug clearance:* Sirolimus is metabolized through the hepatic mixed-function oxidase system (CYP3A4) and excreted through the liver, although both the kidney and the gut may contribute to its elimination. Various medications are known to either increase or decrease sirolimus concentrations by either inhibiting or inducing the CYP3A4 system.
- *Monitoring for drug/drug interactions:* Because sirolimus is metabolized through the CYP3A4 system, drugs that affect this system will affect clearance of sirolimus. A list of the medications that either induce or inhibit the CYP3A4 system are listed in Table 11. In addition, sirolimus is an inhibitor of CYP3A4 and may reduce the clearance of several medications, including digoxin, colchicine, and the HMG-CoA reductase inhibitors. Levels should be checked 3 to 4 days after loading and 7 to 14 days after dose adjustment. Clinicians should consider not using the drug for the first 3 months after transplant because of concerns about dehiscence.
- *Prophylaxis against infections:* Prophylaxis against *P. jiroveci* should be implemented with the use of sirolimus. Prophylaxis recommendations are discussed in Table 12.
- *Monitoring for pulmonary toxicity:* Sirolimus has been associated with pneumotoxic reactions. If patients develop respiratory symptoms while receiving sirolimus therapy, sirolimus pulmonary toxicity is a possible cause.

The following topics have been identified for prioritization for future research regarding sirolimus:

- *The optimal approach to monitoring blood levels of sirolimus.*
- *The frequency of monitoring blood work and sirolimus levels.*

Information for patients:

- *Adverse events associated with sirolimus include anemia, high BP, fluid retention and edema, joint pain, headache, increased cholesterol levels, liver problems, blood clots, and stomach discomfort.*

Recommendations for the monitoring of mTOR inhibitors in patients with lung disease and lung transplant recipients:

3.6a. For patients who will undergo mTOR inhibitor therapy, obtaining cholesterol and triglyceride levels prior to treatment is recommended (Grade 1B).

3.6b. For patients who present with an abnormal elevation of fasting triglycerides, avoidance of mTOR therapy or careful monitoring of triglycerides is recommended (Grade 1B).

3.6c. For patients who undergo mTOR therapy, monitoring for hyperlipidemia is recommended (Grade 1A).

3.6d. For patients who undergo mTOR therapy, monitoring of CBC counts, creatinine, and BP is recommended (Grade 1B).

3.6e. For patients who undergo sirolimus therapy, monitoring of drug concentration is recommended (Grade 1B).

3.6f. For lung transplant recipients scheduled to undergo sirolimus therapy, administration of sirolimus during the early perioperative period is contraindicated due to the risk of airway dehiscence (Grade 1A).

3.6g. For patients who undergo sirolimus therapy and are at risk for poor wound healing, consideration of dose adjustments or an alternative therapy to lower this risk is suggested (Grade 2C).

3.6h. For patients who undergo sirolimus therapy and develop new or worsening respiratory symptoms or signs, an evaluation for sirolimus-induced pulmonary toxicity is recommended (Grade 1B).

3.7 Other Immunosuppressive Drugs

3.7.1 Chloroquine and Hydroxychloroquine: Besides antimalarial properties, chloroquine and hydroxychloroquine have antiinflammatory characteristics.⁵⁵² Hydroxychloroquine has been preferred over chloroquine as an antiinflammatory because given in the higher doses compared with antimalarial properties, hydroxychloroquine may cause less ocular toxicity than chloroquine.⁵⁵³ Table 38 compares the toxicity of chloroquine to hydroxychloroquine. Table 39 summarizes the 11 reports of using an antimalarial agent for sarcoidosis⁵⁵⁴⁻⁵⁶³ along with one series of use of these drugs for pulmonary fibrosis.⁵⁶⁴

3.7.1.1 Toxicity—Chloroquine toxicity is most frequently encountered when parenteral routes are

used to treat comatose patients with malaria. Cardiovascular effects may progress through vasodilation, hypotension, suppressed myocardial function, cardiac arrhythmia, and cardiac arrest.^{566,567} CNS effects may progress through confusion, convulsions, and coma.⁵⁶⁸ Chloroquine seems more likely to cause cardiac disturbances, including heart block and cardiomyopathy, than hydroxychloroquine.⁵⁶⁹⁻⁵⁷¹ Some clinicians perform yearly ECGs in asymptomatic patients taking antimalarial drugs, especially chloroquine.⁵⁷²

Oral therapy may cause GI upset, headache, visual disturbances, urticaria, and pruritus. Prolonged medication use may cause headache; blurring of vision; diplopia; confusion; convulsions; lichenoid skin eruptions; bleaching of the hair; and ECG abnormalities, such as widening of the QRS interval and T-wave changes. These side effects reverse with discontinuation of therapy. Chloroquine may also cause discoloration of the nail beds and mucous membranes and interfere with selected vaccines.⁵⁷³⁻⁵⁷⁵

Chloroquine and hydroxychloroquine, when used as an antiinflammatory agent for chronic diseases, may develop toxic effects with irreversible retinopathy and ototoxicity if oral doses of chloroquine or hydroxychloroquine exceed 250 mg/d.⁵⁷⁶ Similar toxicity has been reported, although less frequently, with hydroxychloroquine.^{554,577} Prolonged therapy with either can cause toxic myopathy, cardiomyopathy, and peripheral neuropathy; these reactions improve if the drug is promptly withdrawn.⁵⁷⁸

3.7.1.1.1 Pediatrics: The antimalarial agents have been used for rheumatologic diseases in children for many years. Although these drugs are generally believed to be safe, there is limited information.⁵⁷⁹

3.7.1.1.2 Ocular Screening: Routine ocular screening has been recommended for patients receiving antimalarial agents. The frequency is every 6 to 12 months.^{553,580,581}

3.7.1.2 Pregnancy—Hydroxychloroquine has been administered during pregnancy. In one study of patients with connective tissue disease, 133 pregnancies in women being treated with hydroxychloroquine resulted in 117 live births.⁵⁸² This was compared with 70 consecutive pregnancies in 53 women with similar disorders who did not receive hydroxychloroquine.⁵⁸² There was no difference in rate of live births or complications from pregnancy.⁵⁸² The authors concluded that giving hydroxychloroquine was safe during pregnancy if clinically indicated by the disease.⁵⁸²

3.7.1.3 Monitoring—Monitoring for ocular toxicity due to chloroquine and hydroxychloroquine has been recommended for every 6 to 12 months.^{553,580,581,583}

Considerations for clinicians regarding chloroquine and hydroxychloroquine for patients with lung disease and lung transplant recipients:

Table 38—Summary of Chloroquine/Hydroxychloroquine Toxicity

Toxicity	Chloroquine	Hydroxychloroquine
Contraindications	Hypersensitivity to drug class or compound components Retinal field changes	Hypersensitivity to drug class or compound components Retinal field changes Visual field changes Psoriasis Pregnancy
Cautions	Long-term use Psoriasis Porphyria Pregnancy G6PD deficiency Hearing impairment Impaired liver function Alcoholism Seizure history	Impaired liver function Alcoholism Hepatotoxic agent use
Drug/drug interactions		
Contraindicated with	Topical benzocaine; butamben; tetracaine, lidocaine; prilocaine topical in infants aged < 1 y because of risk of methemoglobinemia; pimozide; and ranolazine, which may increase risk of QT prolongation with resulting cardiac dysrhythmias	...
Avoid or use alternative	Amiodarone, increased QT interval Azithromycin QT Cimetidine QT Ciprofloxacin QT Clarithromycin QT Clozapine QT, increase clozapine level, seizures Dasatinib QT Dronedarone QT Droperidol QT Erythromycin QT Fluconazole QT Haloperidol QT Lapatinib QT Methadone QT Paliperidone QT Penicillamine, increase penicillamine level, severe hematologic and renal toxicity Pentamidine QT Posaconazole QT Sodium phosphate QT, electrolyte abnormalities Tacrolimus QT Tamoxifen, increase tamoxifen level Telbivudine myopathy Telithromycin QT Voriconazole QT Vorinostat QT	Penicillamine, increase penicillamine level; severe hematologic and renal toxicity Telbivudine myopathy Haloperidol QT Metoprolol arrhythmias
Monitor or modify treatment	Antacids β 2-agonists Cyclosporine Mefloquine Penicillins	...

(Continued)

- *Monitoring blood work:* Studies of chloroquine and hydroxychloroquine therapy have suggested a CBC count and liver function study initially and every 6 to 12 months. Patients should undergo an ocular examination at least once a year. Because these drugs can cause heart block and

cardiomyopathy, patients with unexplained cardiac symptoms should be considered for echocardiogram and ECG.

- *Monitoring of drug clearance:* Chloroquine and hydroxychloroquine are both cleared by the kidneys. They have prolonged half-lives (> 1 month).

Table 38—Continued

Toxicity	Chloroquine	Hydroxychloroquine
Caution advised	Topical benzocaine, butamben, tetracaine, lidocaine, prilocaine topical: combination may increase risk of methemoglobinemia Acetaminophen/tramadol Apomorphine Benzocaine topical Botulinum toxins Bupropion Cimetidine Lindane topical Nitroprusside Praziquantel Propafenone Pyridostigmine Solifenacin Tiagabine Tramadol	Botulinum toxins Digoxin Propafenone
Adverse reactions		
Serious reactions	Ocular toxicity Auditory toxicity Seizures	Agranulocytosis Thrombocytopenia
Common reactions		
Other information		
Pregnancy class	C	C
Metabolism	Liver, partially	Liver, partially
Excretion	Urine, 95% (45% unchanged) Bile	Renal, 25% unchanged Bile

G6PD = glucose-6-phosphate dehydrogenase.

- *Monitoring for drug/drug interaction:* Chloroquine and hydroxychloroquine have potentially significant interactions with D-penicillamine and cimetidine, leading to higher levels of drug.
- *Prophylaxis against infections:* There are no special issues for chloroquine and hydroxychloroquine. Prophylaxis recommendations are discussed in Table 12.

The following topics have been identified for prioritization for future research regarding chloroquine and hydroxychloroquine:

- *The need for infection prophylaxis.*
- *The appropriate strategy for monitoring for cardiac toxicity.*

Information for patients:

- *Check your temperature frequently and report a fever to your physician immediately.*
- *Report to your physician signs of infection, such as cough, aches, fever, and chills; a wound or cut with redness, pain, discharge, or pus; pain; burning with urination; and nausea, vomiting, and diarrhea.*
- *Report any changes in your vision.*
- *Report any passing out spells or signs of heart failure, such as unexplained severe leg swelling.*

3.7.2 Imatinib Mesylate Oral: Imatinib mesylate is a protein-tyrosine kinase inhibitor that inhibits proliferation and induces apoptosis in a variety of abnormal cell lines.⁵⁸⁴ Currently, the drug is licensed to treat chronic myeloid leukemia.⁵⁸⁴ Imatinib also is licensed to treat GI stromal tumor.⁵⁸⁴ Imatinib mesylate has been used in fibrotic lung diseases⁵⁸⁵ and pulmonary arterial hypertension.^{586,587} Table 40 summarizes the incidence of various toxicities reported with imatinib use.^{588,589} Table 41 summarizes four randomized trials examining the use of imatinib for nonpulmonary indications.⁵⁸⁸⁻⁵⁹¹ All these studies provided important information regarding toxicity.

3.7.2.1 Toxicity—Bullous dermatologic reactions, including erythema multiforme and Stevens-Johnson syndrome, have been seen with this drug.⁵⁹² Significant fluid retention is seen after drug initiation and may manifest as pleural effusions, ascites, pulmonary edema, and peripheral edema.⁵⁹² Fluid retention is more commonly seen in patients aged >65 years.⁵⁹² GI irritation has been seen and is decreased by taking the medication with food and a large glass of water.⁵⁹² Hemorrhage, usually of GI origin, has been reported.⁵⁹²

Neutropenia, anemia, and thrombocytopenia are seen after imatinib therapy.⁵⁹³ The FDA package insert recommends a CBC count weekly for the first month, biweekly for the second month, and periodically thereafter as clinically indicated (eg, every

Table 39—Monitoring of Chloroquine and Hydroxychloroquine

Author/Year	Study Design	Disease	Dose	Route	No. Patients	Age	Duration of Therapy	Duration of Monitoring	Complications Noted	Study Adequacy	Comments
Morse et al ^{555/1961}	PS, open clinical trial	Sarcoidosis, cutaneous	CQ 500 mg	Oral	7	NA	6 mo	6 mo	Transient corneal opacity	3	Five of seven with pulmonary lesions Cutaneous lesions improved markedly Pulmonary lesions less consistent improvement
Hirsch ^{556/1961}	CS	Sarcoidosis, cutaneous and pulmonary	CQ 500 mg	Oral	8	NA	6 mo	6 mo	No complications reported	1	Cutaneous in seven of eight Pulmonary lesions in six of eight Cutaneous lesions improved markedly Pulmonary lesions less consistent improvement
Davies ^{556/1963}	CS	Sarcoidosis, pulmonary	CQ 400-600 mg		5	NA	1-2 y	2 y	All had reversible bleaching of hair	3	Two showed improvement Two no change One died
Siltzbach and Teirstein ^{557/1964}	PS, open clinical trial	Sarcoidosis, pulmonary and cutaneous	CQ 500 mg	Oral	43	NA	4-17 mo	2 y	Anorexia, vertigo, pruritus, transient diplopia	3	Cutaneous lesions in 14 of 43 31 of 43 pulmonary lesions improved 14 of 14 skin lesions improved
Krasnitz ^{559/1967}	CO clinical trial	Sarcoidosis, pulmonary	CQ 500 mg	Oral	30	NA	6 mo	1 y	Nausea, GI upset (n = 9) Reversible corneal change (n = 1)	3	15 of 21 showed improvement
Brodthagen ^{560/1968}	CS	Sarcoidosis, cutaneous and pulmonary	HCQ 500-1,000 mg	Oral	15	NA	NA	NA	None noted	1	Pulmonary, 12 of 15
Davies and Curwen ^{558/1967}	RCT, DB	Sarcoidosis, pulmonary	CQ 600 mg × 2 mo then 400 mg × 2 mo	Oral	57	NA	4 mo	4 mo	GI upset (n = 5) Transient visual changes (n = 10) Corneal lesions (n = 4) Headache and vertigo (n = 6) Bleached hair	3	...

(Continued)

Table 39—Continued

Author/Year	Study Design	Disease	Dose	Route	No. Patients	Age	Duration of Therapy	Duration of Monitoring	Complications Noted	Study Adequacy	Comments
O'Leary et al ⁵⁶³ /1986	CS	Sarcoidosis, calcium metabolism	CQ 500 mg/d	Oral	2	NA	6-10 mo	3 y	None noted	1	...
Johns ⁵⁶¹ /1986	Open clinical trial	Sarcoidosis	CQ 500 mg × 2 wk then 250 × 6 mo	Oral	25	NA	8 mo	8 mo	No complications reported	3	...
Jones and Callen ⁵⁶⁵ /1990	Open clinical trial	Sarcoidosis, cutaneous	HCQ 200-400 mg for ≥ 3 mo	Oral	17	NA	3 mo	1 y	Nausea and vomiting (n = 2)	3	Pulmonary, 8 of 17; ocular, 1 of 17; hepatic, 1 of 17
Osika et al ⁵⁶⁴ /1997	CS	Pulmonary fibrosis	HCQ 10 mg/kg/d	Oral	NA	1.5-12 mo	1.5-12 mo	NA	Both patients died of progressive disease	1	Initial treatment with prednisone 2 mg/kg/d HCQ added with either colchicine 1 mg/d (one patient) or CYC 100 mg/d (one patient)
Baltzan et al ⁵⁶³ /1999	PRCT, OL, SC	Pulmonary sarcoidosis	Run in phase: CQ 750 mg/d × 2 mo, 500 mg/d × 2 mo, 250 mg/d × 2 mo, then randomized to observation without drug vs maintenance at 250 mg/d	Oral	23	29-67 y	6 mo	6 mo	Intolerable dose-related side effects (abdominal pain with vomiting in two subjects, destabilization of a preexisting anxiety disorder in one subject) Retinopathy suspected in one subject with CQ discontinued	5	Organs involved at baseline (skin, lymph node, spleen) generally improved

See Table 5-7, 11, and 33 legends for expansion of abbreviations.

Table 40—Monitoring of Imatinib Mesylate (Adverse Events)^a

Side Effect	Incidence/1,000	Monitoring Used
Anemia	889	Weekly hemogram for 1 mo, biweekly for the second month, and then periodically
Neutropenia	408	...
Thrombocytopenia	60	...
Edema	575-715	...
Fatigue	370-679	...
Fever	119-154	...
Pruritis	162	...
Rash	266-372	...
Anorexia	260	...
Constipation	160	...
Diarrhea	385-481	...
Abdominal pain	299	...
Nausea	470-509	...
Vomiting	205-264	...
Bleeding	15-109	...
Infection	111-172	...
Dizziness	111-158	...
Arthralgia	130-303	...
Headache	160-336	...
Myalgias and muscle cramps	225-432	...
Pleuritic pain	511	...
Cough	130-174	...
Dyspnea	115	...
Nasopharyngitis	269	...
Insomnia	132	...
Depression	127	...
Renal or genitourinary	132	...

^aSide effects at 400 mg/d seen in > 10% of patients, with ranges calculated from O'Brien et al⁵⁹⁸ and Verweij et al.⁵⁹⁹

2-3 months).⁵⁹³ Specific dose reduction or treatment interruptions for severe neutropenia and thrombocytopenia are suggested in the package insert.⁵⁹³

Hepatic impairment, occasionally severe, has been seen with imatinib mesylate. The FDA package insert recommends liver function monitoring (eg, transaminase, bilirubin, alkaline phosphatase levels) before initiation of treatment and monthly or as clinically indicated.⁵⁹³

There are insufficient data to determine whether lymphoma or nonlymphomatous malignancies are increased as a result of using imatinib mesylate, although some carcinogenesis, mutagenesis, and impairment of fertility studies are suggestive. Case reports of drug-induced pneumonitis^{594,595} have not been seen in the RCTs for cancers, although dyspnea has been recorded.

3.7.2.2 Pregnancy—Imatinib is classified as category D by the FDA.⁵⁹² There is evidence of increased fetal risk, and risk vs benefit should be considered for use during pregnancy.⁵⁹⁶ Animal studies suggest potential teratogenicity.⁵⁹⁶ Imatinib can enter breast

milk in animals and has been detected in breast milk in humans.⁵⁹⁶

3.7.2.3 Monitoring—The manufacturer recommends a CBC count weekly for the first month of therapy, biweekly for the second month, and then periodically.⁵⁹² Liver function testing is recommended at baseline and at subsequent monthly intervals.⁵⁹²

Considerations for clinicians regarding imatinib mesylate for patients with lung disease and lung transplant recipients:

- *Monitoring blood work:* CBC count and hepatic function should be monitored every 1 to 3 months as long as patients are receiving therapy.
- *Monitoring of drug clearance:* No monitoring is suggested at this time.
- *Monitoring for drug/drug interaction:* Many drugs alter hepatic clearance of imatinib mesylate by inducing the CYP3A4 pathway, and dosing alterations should be considered with drugs and remedies, such as warfarin sodium, some herbal products (St. John's wort), rifampin, erythromycin, metoprolol, ketoconazole, grapefruit juice, and phenytoin. Imatinib can affect thyroid replacement needs and thyroid levels should be monitored in patients with hypothyroidism. Other drug interactions are listed in Table 11.
- *Prophylaxis against infections:* There are no special issues for imatinib mesylate. Prophylaxis recommendations are discussed in Table 12.

The following topics have been identified for prioritization for future research regarding imatinib mesylate:

- Activity of imatinib mesylate against nonmalignant lung diseases.
- The need for prophylaxis against *P jiroveci*.
- How frequently one needs to monitor CBC count and hepatic function.

Recommendations for the monitoring of other immunosuppressive drugs in patients with lung disease and lung transplant recipients:

3.7a. For patients receiving hydroxychloroquine and chloroquine, an eye examination at least once per year is suggested (Grade 2B).

3.7b. For patients who undergo imatinib mesylate therapy, monitoring of CBC and hepatic function is suggested (Grade 2C).

4.0 DISCUSSION

All the drugs discussed in this guideline have the potential to cause serious harm to patients, and most

Table 41—Monitoring of Imatinib Mesylate

Author/Year	Study Design	Disease	Dose	Route	No. Patients Treated	Age, y	Duration of Therapy	Duration of Monitoring	Complications Noted	Study Adequacy	Comments Malignancy/Death Pregnancy
O'Brien et al ^{585/2003}	DB, RCT	Newly diagnosed chronic phase CML	400 mg	Oral	551	18-70	24 mo	24 mo	Superficial edema; dyspepsia; pharyngolaryngeal pain; URI all numerically more numerous than comparators	4	Superior 24-mo progression-free survival compared with interferon and cytarabine
Verweij et al ^{586/2004}	DB, RCT	Advanced GISTs	400 mg/d vs 400 mg bid	Oral	946	18-91	30 mo	30 mo	Statistically more edema, anemia, rash, fatigue, nausea, bleeding, diarrhea, and dyspnea seen in the 400 mg bid group	4	Full listing of all adverse events shows more events in the 400 mg bid group
Zohlnhöfer et al ^{589/2005}	DB, PRCT	Coronary artery disease with in-stent restenosis	600 mg	Oral	80	NR	10 d	1 y	Cr level elevation; nausea; vomiting; diarrhea; skin rash; pruritis	5	No efficacy for coronary stent restenosis rate
Van Glabbeke et al ^{590/2006} ^a	DB, RCT	Advanced GISTs	400 mg/d vs 400 mg bid	Oral	946	18-91	30 mo	30 mo	SAEs included deaths from drug toxicity (n = 2), infection (n = 3), hemorrhage (n = 3), severe diarrhea and vomiting (n = 1), and cardiac disease (n = 2)	4	No difference in death from complications between treatment groups

CML = chronic myelogenous leukemia; GIST = GI stromal cell tumor. See Table 5, 6, 8, 9, and 24 legends for expansion of other abbreviations.

^aSame cohort as Verweij et al.⁵⁸⁶

Table 42—Summary of Adverse Reactions by Specific Drugs

Drug Class	Specific Drug	Infusion React	Infection	Bone Marrow	Renal Funct	Nervous Sys	GI	Hepatic	Genito-urinary	CV	Lipid Metab	Malignancy	Pulm Tox	Ocular Tox	Skin React	Wound Heal	Pregnancy Class (FDA)
Anti-TNF agents	Adalimumab		+			+						NA	±				B
	Etanercept		+			+		±					±				B
	Infliximab		+	±		±		±					±				B
CNIs	CsA		++	+	++	+	+	+		+							C
	Tacrolimus		++	+	++	+	+	+		+	+						C
Cytolytic antibodies	Alemtuzumab	+	++	+													C
	ATG	+	++	+			+	+		+							C
	Muromonab	+	++	+		+		+		+							C
	Rituximab	+	+	+		+		+					±				C
IL-2 antagonists	Basiliximab	+	+														B
	Daclizumab	+	+			+		+		±							C
Cytotoxic agents	AZA		+	+		+	+	++					+				D
	CYC		+	++			+	+	++			+	+				D
	Leflunomide		+	+		+	+	+		+			+				X
	MTX		+	+				++		+			+				X
mTOR inhibitors	MPA derivatives		+	+		+	+	+					+				D
	Everolimus		+	+							++						...
Other agents	Sirolimus		+	+				+		+	++					+	C
	CQ/HCQ	+	+	+		+	+	+		+				+	+		D
	Imatinib mesylate		+	+		+	+	+					+		+		D

Pregnancy categories: A = controlled studies in women fail to demonstrate a risk to the fetus in the first trimester (and there is no evidence of a risk in later trimesters), and the possibility of fetal harm appears remote; B = either animal reproduction studies have not demonstrated a fetal risk, but there are no controlled studies in pregnant women or animal reproduction studies have shown adverse effects (other than a decrease in fertility) that were not confirmed in controlled studies in women in the first trimester (and there is no evidence of a risk in later trimesters); C = either studies in animals have revealed adverse effects on the fetus (teratogenic, embryocidal, other) and there are no controlled studies in women or studies in women and animals are not available; drugs should be given only if the potential benefit justifies the potential risk to the fetus; D = there is positive evidence of human fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk (eg, if the drug is needed in a life-threatening situation or for a serious disease for which safer drugs cannot be used or are ineffective); X = studies in animals or human beings have demonstrated fetal abnormalities, there is evidence of fetal risk based on human experience, or both, and the risk of the use of the drug in pregnant women clearly outweighs any possible benefit; the drug is contraindicated in women who are or may become pregnant. CV = cardiovascular; FDA = Food and Drug Administration. See Table 5-9, and 11 legends for expansion of other abbreviations.

can affect multiple organ systems and may have synergistic effects when used in combination with other immunosuppressive agents (eg, a calcineurin inhibitor plus a cytotoxic agent for prophylaxis of lung allograft rejection). A summary of data on adverse reactions is presented in Table 42. Recognizing and following our recommendations may enable health-care providers to optimally monitor patients treated with these agents, avoid complications caused by drug toxicity, and detect adverse reactions in a timely manner such that harm can be prevented or limited.

Infection is a major complication that can occur as a consequence of administering these immunosuppressive drugs and reactivation of latent disease (eg, TB, herpesviruses, endemic fungi) or the onset of new infection (eg, aspergillosis, histoplasmosis, other endemic fungi, *Pneumocystis* pneumonia, CMV pneumonia, viral hepatitis) during the course of treatment present significant risks for patients. Infection may occur because of suppression of immune cell function (eg, T lymphocytes), bone marrow toxicity with cytopenias (eg, neutropenia), or a combination of depressed cell function and decreased numbers of immune effector cells. Intense combination therapy with more than one immunosuppressive agent is likely to further increase the risk for opportunistic infection, and lung transplant recipients are typically given prophylactic therapies to prevent infections with CMV and other DNA viruses, *P jiroveci*, and *Aspergillus* (Table 12). When patients are given combination therapy (eg, calcineurin inhibitor, antineoplastic cytotoxic agent, and prednisone for lung transplant recipients), the identification of infection risks attributable to a specific agent are difficult to discern. Potent immunosuppressive regimens used in lung transplant recipients could lead to disease reactivation, and these patients should be uniformly and carefully screened for evidence of active or latent TB prior to wait listing for lung transplantation. Additionally, if intensive immunosuppressive therapy that is similar to that used for lung transplant recipients is used for indications other than a lung transplant, prophylaxis for *P jiroveci* should be strongly considered.

Many of these agents, particularly the cytotoxic drugs, can depress bone marrow function. Granulocytic cell lines are most susceptible, and neutropenia may complicate therapy by predisposing patients to infection. Other hematopoietic cell lineages may also be affected and lead to anemia or thrombocytopenia. Additionally, drug combinations such as a calcineurin inhibitor plus a cytotoxic agent given for posttransplant immunosuppression may have additive effects, and other drugs (eg, trimethoprim/sulfamethoxazole or ganciclovir) given for prophylaxis or treatment of

infection may contribute to bone marrow suppression and potentiate the effect of immunosuppressive drug therapies. Intermittent monitoring of bone marrow function through CBC with differential cell count is advised for all patients receiving drugs that are associated with potential bone marrow suppression.

Monitoring blood levels is essential for the calcineurin and mTOR inhibitors to avoid various toxicities, particular kidney damage and bone marrow suppression. Additionally, the calcineurin inhibitors have numerous potential drug/drug interactions, and blood levels should be checked serially when other drugs known to interact with calcineurin inhibitors are prescribed or the doses of simultaneously administered drugs are increased or decreased to avoid loss of immunosuppressive efficacy by the calcineurin inhibitor (eg, a CYP3A4 inducer) or increased calcineurin blood level and effects (eg, a CYP3A4-metabolized drug that inhibits calcineurin inhibitor metabolism).

Many of these drugs, particularly antilymphocyte antibodies that are administered by IV, have the potential to cause infusion reactions that can be severe and have systemic consequences, including anaphylaxis, systemic hypotension, cardiac dysfunction, and severe third spacing of fluid as in acute pulmonary edema. Patients who receive these drugs must be monitored carefully, especially when they have previously received such therapies and may mount an acute hypersensitivity response if they have been sensitized by previous exposures.

GI toxicity, including severe hepatotoxicity, can occur as a consequence of a number of these drugs. The calcineurin inhibitors and MPA derivatives can significantly affect intestinal transit times and often cause diarrhea, which can be severe in some instances and not necessarily correlate well with blood levels of the calcineurin inhibitors. Although blood levels of mycophenolate are not routinely obtained to monitor this agent, if diarrhea complicates therapy, a blood level may be useful. Serious hepatic injury can occur with some of these agents, especially prolonged therapy with methotrexate or azathioprine, and hepatic function should be intermittently monitored (eg, once monthly) with appropriate testing while patients are receiving agents that can potentially cause serious hepatotoxicity.

Many drug/drug interactions can occur with these agents and are summarized in Table 11. Knowledge of drug/drug interactions is essential when new drugs are administered as well as when coadministered drugs are withdrawn or doses are altered. This is particularly important for drugs that are metabolized by the CYP3A4 enzyme system because many commonly prescribed agents (eg, imidazole antifungal agents, macrolide antibiotics) can significantly affect blood

levels of the calcineurin inhibitors, mTOR inhibitors, and imatinib mesylate. Additionally, the majority of the agents covered in this guideline can suppress antibody responses to vaccines that do not use live viruses (eg, herpes zoster, nasal influenza), and recipients may be endangered if given live virus vaccines while receiving immunosuppression. Lastly, potentially significant interactions have been documented for some of these agents, with ingested substances such as grapefruit juice, *Echinacea*, and herbal preparations or supplements, and patients should be aware of these potential interactions.

Most of the drugs covered in this guideline are in the FDA categories of C, D, or X, and none of these drugs have been assigned to category A. Pregnancy should be avoided when patients are taking these medications, and these agents should not be prescribed for pregnant women unless the treatment benefit clearly outweighs the risk of teratogenic effects on the developing fetus.

Although many of the agents discussed in this guideline have been prescribed for pediatric patients, prescribing and safety data emanating from the treatment of pediatric patient populations are relatively limited for inflammatory lung disease and for lung transplant recipients. Although many of the observations and recommendations in this guideline may apply to pediatric patients, caution must be exercised when using these agents, particularly in young children.

In summary, the use of immunosuppressive agents covered in this guideline can be associated with serious harm to patients receiving such therapy and need to be monitored carefully. Although toxicity data based on clinical trials in large cohorts of patients with inflammatory lung disease or in lung transplant recipients (which could guide pulmonologists in the prescription of these drugs) are relatively lacking, there is enough literature to support the guidelines presented here. This guideline statement can be used as a resource to guide the administration of these potent immunosuppressive agents in a manner that minimizes potential harm to patients through awareness of potential toxicities, drug/drug interactions, and appropriate monitoring protocols.

ACKNOWLEDGMENTS

Author contributions: Dr Baughman is the guarantor of the manuscript. All authors contributed equally to the guidelines and the executive summary.

Dr Baughman: contributed to the design, execution, and review of the guidelines.

Dr Meyer: contributed to the design, execution, and review of the guidelines.

Dr Nathanson: contributed to the design, execution, and review of the guidelines.

Dr Angel: contributed to the design, execution, and review of the guidelines.

Dr Bhorade: contributed to the design, execution, and review of the guidelines.

Dr Chan: contributed to the design, execution, and review of the guidelines.

Dr Culver: contributed to the design, execution, and review of the guidelines.

Mr Harrod: contributed to the design, execution, and review of the guidelines.

Dr Hayney: contributed to the design, execution, and review of the guidelines.

Dr Highland: contributed to the design, execution, and review of the guidelines.

Dr Limper: contributed to the design, execution, and review of the guidelines.

Dr Patrick: contributed to the design, execution, and review of the guidelines.

Dr Strange: contributed to the design, execution, and review of the guidelines.

Dr Whelan: contributed to the design, execution, and review of the guidelines.

Financial/nonfinancial disclosures: The authors have reported to *CHEST* the following conflicts of interest: Dr Baughman's institution (University of Cincinnati) has received grants for research in sarcoidosis and idiopathic pulmonary fibrosis from Actelion Pharmaceuticals Ltd; Celgene Corporation; Cephalon, Inc; Centocor Ortho Biotech, Inc; Gilead Sciences, Inc; and InterMune. Dr Hayney has received grant support from the University of Wisconsin and the National Institutes of Health. She serves on the speakers' bureau for Merck Vaccines. Dr Patrick received a travel stipend from Omneotech, Inc; owns stock in pharmaceutical/medical device companies, including Human Economics, Rite Aid Corp, Numec, and Hospira, Inc; and is a member of the speakers' bureau for Gilead Sciences, Inc. Dr Strange has received grant monies and salary support from the National Institutes of Health to study cyclophosphamide and mycophenolate mofetil in scleroderma. He has received grant monies and salary support from Centocor Ortho Biotech, Inc, for the study of ustekinumab and golimumab in sarcoidosis. He has been a consultant for AstraZeneca; Uptake Medical; PneumRx, Inc; Pulmonx; Aeris Therapeutics; Talecris Biotherapeutics Inc; CSL Behring; Baxter; Gilead Sciences, Inc; MedImmune, LLC; and Actelion Pharmaceuticals Ltd in the past 3 years. For the past 3 years, he has received speakers' bureau income from AstraZeneca; Talecris Biotherapeutics, Inc; Gilead Sciences, Inc; Actelion Pharmaceuticals Ltd; and Pfizer, Inc, and from the France Foundation for InterMune on topics not related to the subject of this article. Dr Whelan has received research support from Actelion Pharmaceuticals Ltd; Celgene Corporation; Centocor Ortho Biotech, Inc; and InterMune. He has also received consultant fees from InterMune. His contributions to this article were free from potential conflicts of interest related to these activities. Drs Meyer, Nathanson, Angel, Bhorade, Chan, Culver, Highland, and Limper and Mr Harrod have reported that no potential conflicts of interest exist with any companies/organizations whose products or services may be discussed in this article.

REFERENCES

- Jadad AR, McQuay HJ. A high-yield strategy to identify randomized controlled trials for systematic reviews. *Online J Curr Clin Trials*. 1993;(33).
- Breedveld FC, Weisman MH, Kavanaugh AF, et al. The PREMIER study: a multicenter, randomized, double-blind clinical trial of combination therapy with adalimumab plus methotrexate versus methotrexate alone or adalimumab alone in patients with early, aggressive rheumatoid arthritis who had not had previous methotrexate treatment. *Arthritis Rheum*. 2006;54(1):26-37.
- Furst DE, Schiff MH, Fleischmann RM, et al. Adalimumab, a fully human anti tumor necrosis factor- α monoclonal antibody, and concomitant standard antirheumatic therapy for the treatment of rheumatoid arthritis: results of STAR (Safety Trial of Adalimumab in Rheumatoid Arthritis). *J Rheumatol*. 2003;30(12):2563-2571.

4. Weinblatt ME, Keystone EC, Furst DE, Kavanaugh AF, Chartash EK, Segurado OG. Long term efficacy and safety of adalimumab plus methotrexate in patients with rheumatoid arthritis: ARMADA 4 year extended study. *Ann Rheum Dis*. 2006;65(6):753-759.
5. Weinblatt ME, Keystone EC, Furst DE, et al. Adalimumab, a fully human anti-tumor necrosis factor alpha monoclonal antibody, for the treatment of rheumatoid arthritis in patients taking concomitant methotrexate: the ARMADA trial. *Arthritis Rheum*. 2003;48(1):35-45.
6. Genovese MC, Mease PJ, Thomson GT, et al; M02-570 Study Group. Safety and efficacy of adalimumab in treatment of patients with psoriatic arthritis who had failed disease modifying antirheumatic drug therapy. *J Rheumatol*. 2007;34(5):1040-1050.
7. Mease PJ, Gladman DD, Ritchlin CT, et al; Adalimumab Effectiveness in Psoriatic Arthritis Trial Study Group. Adalimumab for the treatment of patients with moderately to severely active psoriatic arthritis: results of a double-blind, randomized, placebo-controlled trial. *Arthritis Rheum*. 2005;52(10):3279-3289.
8. Menter A, Tying SK, Gordon K, et al. Adalimumab therapy for moderate to severe psoriasis: a randomized, controlled phase III trial. *J Am Acad Dermatol*. 2008;58(1):106-115.
9. Lambert RG, Salonen D, Rahman P, et al. Adalimumab significantly reduces both spinal and sacroiliac joint inflammation in patients with ankylosing spondylitis: a multicenter, randomized, double-blind, placebo-controlled study. *Arthritis Rheum*. 2007;56(12):4005-4014.
10. van der Heijde D, Kivitz A, Schiff MH, et al; ATLAS Study Group. Efficacy and safety of adalimumab in patients with ankylosing spondylitis: results of a multicenter, randomized, double-blind, placebo-controlled trial. *Arthritis Rheum*. 2006;54(7):2136-2146.
11. Sandborn WJ, Hanauer SB, Rutgeerts P, et al. Adalimumab for maintenance treatment of Crohn's disease: results of the CLASSIC II trial. *Gut*. 2007;56(9):1232-1239.
12. Sandborn WJ, Rutgeerts P, Enns R, et al. Adalimumab induction therapy for Crohn disease previously treated with infliximab: a randomized trial. *Ann Intern Med*. 2007;146(12):829-838.
13. Baughman RP, Lower EE. Novel therapies for sarcoidosis. *Semin Respir Crit Care Med*. 2007;28(1):128-133.
14. Callejas-Rubio JL, Ortego-Centeno N, Lopez-Perez L, Benticuaga MN. Treatment of therapy-resistant sarcoidosis with adalimumab. *Clin Rheumatol*. 2006;25(4):596-597.
15. Heffernan MP, Smith DI. Adalimumab for treatment of cutaneous sarcoidosis. *Arch Dermatol*. 2006;142(1):17-19.
16. Philips MA, Lynch J, Azmi FH. Ulcerative cutaneous sarcoidosis responding to adalimumab. *J Am Acad Dermatol*. 2005;53(5):917.
17. Marnane M, Lynch T, Scott J, Stack J, Kelly PJ. Steroid-unresponsive neurosarcoidosis successfully treated with adalimumab. *J Neurol*. 2009;256(1):139-140.
18. Baughman R. Tumor necrosis factor inhibition in treating sarcoidosis: the American experience. *Rev Port Pneumol*. 2007;13:S47-S50.
19. Hyrich K, Symmons D, Watson K, Silman A; BSRBR Control Centre Consortium; British Society for Rheumatology Biologics Register. Baseline comorbidity levels in biologic and standard DMARD treated patients with rheumatoid arthritis: results from a national patient register. *Ann Rheum Dis*. 2006;65(7):895-898.
20. Keane J, Gershon S, Wise RP, et al. Tuberculosis associated with infliximab, a tumor necrosis factor alpha-neutralizing agent. *N Engl J Med*. 2001;345(15):1098-1104.
21. Efde MN, Houtman PM, Spoorenberg JP, Jansen TL. Tonsillar tuberculosis in a rheumatoid arthritis patient receiving anti-TNFalpha (adalimumab) treatment. *Neth J Med*. 2005;63(3):112-114.
22. Sichelidis L, Settas L, Spyrtos D, Chloros D, Patakas D. Tuberculosis in patients receiving anti-TNF agents despite chemoprophylaxis. *Int J Tuberc Lung Dis*. 2006;10(10):1127-1132.
23. Lange C, Hellmich B, Ernst M, Ehlers S. Rapid immunodiagnosis of tuberculosis in a woman receiving anti-TNF therapy. *Nat Clin Pract Rheumatol*. 2007;3(9):528-534.
24. Matulis G, Jüni P, Villiger PM, Gadola SD. Detection of latent tuberculosis in immunosuppressed patients with autoimmune diseases: performance of a *Mycobacterium tuberculosis* antigen-specific interferon gamma assay. *Ann Rheum Dis*. 2008;67(1):84-90.
25. Tubach F, Ravaud P, Salmon-Céron D, et al; Recherche Axée sur la Tolérance des Biothérapies Group. Emergence of *Legionella pneumophila* pneumonia in patients receiving tumor necrosis factor-alpha antagonists. *Clin Infect Dis*. 2006;43(10):e95-e100.
26. Kalyoncu U, Karadag O, Akdogan A, et al. *Pneumocystis carinii* pneumonia in a rheumatoid arthritis patient treated with adalimumab. *Scand J Infect Dis*. 2007;39(5):475-478.
27. van Ingen J, Boeree M, Janssen M, et al. Pulmonary *Mycobacterium szulgai* infection and treatment in a patient receiving anti-tumor necrosis factor therapy. *Nat Clin Pract Rheumatol*. 2007;3(7):414-419.
28. Wolfe F, Caplan L, Michaud K. Treatment for rheumatoid arthritis and the risk of hospitalization for pneumonia: associations with prednisone, disease-modifying antirheumatic drugs, and anti-tumor necrosis factor therapy. *Arthritis Rheum*. 2006;54(2):628-634.
29. Ramos-Casals M, Brito-Zerón P, Muñoz S, et al. Autoimmune diseases induced by TNF-targeted therapies: analysis of 233 cases. *Medicine (Baltimore)*. 2007;86(4):242-251.
30. Allanore Y, Devos-François G, Caramella C, Boumier P, Jounieaux V, Kahan A. Fatal exacerbation of fibrosing alveolitis associated with systemic sclerosis in a patient treated with adalimumab. *Ann Rheum Dis*. 2006;65(6):834-835.
31. Huggett MT, Armstrong R. Adalimumab-associated pulmonary fibrosis. *Rheumatology (Oxford)*. 2006;45(10):1312-1313.
32. Schoe A, van der Laan-Baalbergen NE, Huizinga TW, Breedveld FC, van Laar JM. Pulmonary fibrosis in a patient with rheumatoid arthritis treated with adalimumab. *Arthritis Rheum*. 2006;55(1):157-159.
33. Almodóvar R, Izquierdo M, Zarco P, Javier Quirós F, Mazzucchelli R, Steen B. Pulmonary sarcoidosis in a patient with ankylosing spondylitis treated with infliximab. *Clin Exp Rheumatol*. 2007;25(1):99-101.
34. Sweiss NJ, Baughman RP. Tumor necrosis factor inhibition in the treatment of refractory sarcoidosis: slaying the dragon? *J Rheumatol*. 2007;34(11):2129-2131.
35. Reddy JG, Loftus EV Jr. Safety of infliximab and other biologic agents in the inflammatory bowel diseases. *Gastroenterol Clin North Am*. 2006;35(4):837-855.
36. Stübgen JP. Tumor necrosis factor-alpha antagonists and neuropathy. *Muscle Nerve*. 2008;37(3):281-292.
37. HUMIRA solution for subcutaneous injection, adalimumab solution for subcutaneous injection [package insert]. Abbott Park, IL: Abbott Laboratories; 2008.
38. Hyrich KL, Symmons DP, Watson KD, Silman AJ; British Society, for Rheumatology Biologics Register. Pregnancy outcome in women who were exposed to anti-tumor necrosis factor agents: results from a national population register. *Arthritis Rheum*. 2006;54(8):2701-2702.

39. Hepatitis B reactivation associated with the anti-TNF alpha products ENBREL (etanercept), HUMIRA (adalimumab), and REMICADE (infliximab). Health Canada website. http://www.hc-sc.gc.ca/dhp-mps/alt_formats/pdf/medeff/advisories-avis/prof/2006/anti-tnf_therap_hpc-cps-eng.pdf. Published January 2006. Accessed October 21, 2011.
40. Enbrel, etanercept [package insert]. Thousand Oaks, CA: Immunex Corporation; 2004.
41. Keystone EC, Schiff MH, Kremer JM, et al. Once-weekly administration of 50 mg etanercept in patients with active rheumatoid arthritis: results of a multicenter, randomized, double-blind, placebo-controlled trial. *Arthritis Rheum*. 2004;50(2):353-363.
42. Mathias SD, Colwell HH, Miller DP, Moreland LW, Buatti M, Wanke L. Health-related quality of life and functional status of patients with rheumatoid arthritis randomly assigned to receive etanercept or placebo. *Clin Ther*. 2000;22(1):128-139.
43. van der Heijde D, Klareskog L, Rodriguez-Valverde V, et al; TEMPO Study Investigators. Comparison of etanercept and methotrexate, alone and combined, in the treatment of rheumatoid arthritis: two-year clinical and radiographic results from the TEMPO study, a double-blind, randomized trial. *Arthritis Rheum*. 2006;54(4):1063-1074.
44. Leonardi CL, Powers JL, Matheson RT, et al; Etanercept Psoriasis Study Group. Etanercept as monotherapy in patients with psoriasis. *N Engl J Med*. 2003;349(21):2014-2022.
45. Mease PJ, Goffe BS, Metz J, VanderStoep A, Finck B, Burge DJ. Etanercept in the treatment of psoriatic arthritis and psoriasis: a randomised trial. *Lancet*. 2000;356(9227):385-390.
46. Tying S, Gottlieb A, Papp K, et al. Etanercept and clinical outcomes, fatigue, and depression in psoriasis: double-blind placebo-controlled randomised phase III trial. *Lancet*. 2006;367(9504):29-35.
47. Aboulafia DM, Bundow D, Wilske K, Ochs UI. Etanercept for the treatment of human immunodeficiency virus-associated psoriatic arthritis. *Mayo Clin Proc*. 2000;75(10):1093-1098.
48. Lovell DJ, Giannini EH, Reiff A, et al; Pediatric Rheumatology Collaborative Study Group. Etanercept in children with polyarticular juvenile rheumatoid arthritis. *N Engl J Med*. 2000;342(11):763-769.
49. Calin A, Dijkmans BA, Emery P, et al. Outcomes of a multicentre randomised clinical trial of etanercept to treat ankylosing spondylitis. *Ann Rheum Dis*. 2004;63(12):1594-1600.
50. Gorman JD, Sack KE, Davis JC Jr. Treatment of ankylosing spondylitis by inhibition of tumor necrosis factor alpha. *N Engl J Med*. 2002;346(18):1349-1356.
51. Davis JC Jr, Van Der Heijde D, Braun J, et al; Enbrel Ankylosing Spondylitis Study Group. Recombinant human tumor necrosis factor receptor (etanercept) for treating ankylosing spondylitis: a randomized, controlled trial. *Arthritis Rheum*. 2003;48(11):3230-3236.
52. Raghu G, Brown KK, Costabel U, et al. Treatment of idiopathic pulmonary fibrosis with etanercept: an exploratory, placebo-controlled trial. *Am J Respir Crit Care Med*. 2008;178(9):948-955.
53. Utz JP, Limper AH, Kalra S, et al. Etanercept for the treatment of stage II and III progressive pulmonary sarcoidosis. *Chest*. 2003;124(1):177-185.
54. Baughman RP, Lower EE, Bradley DA, Raymond LA, Kaufman A. Etanercept for refractory ocular sarcoidosis: results of a double-blind randomized trial. *Chest*. 2005;128(2):1042-1047.
55. Seo P, Min YI, Holbrook JT, et al; WGET Research Group. Damage caused by Wegener's granulomatosis and its treatment: prospective data from the Wegener's Granulomatosis Etanercept Trial (WGET). *Arthritis Rheum*. 2005;52(7):2168-2178.
56. Wallis RS, Broder MS, Wong JY, Hanson ME, Beenhouwer DO. Granulomatous infectious diseases associated with tumor necrosis factor antagonists. *Clin Infect Dis*. 2004;38(9):1261-1265.
57. Kwon HJ, Coté TR, Cuffe MS, Kramer JM, Braun MM. Case reports of heart failure after therapy with a tumor necrosis factor antagonist. *Ann Intern Med*. 2003;138(10):807-811.
58. Galaria NA, Werth VP, Schumacher HR. Leukocytoclastic vasculitis due to etanercept. *J Rheumatol*. 2000;27(8):2041-2044.
59. Bleumink GS, ter Borg EJ, Ramselaar CG, Ch Stricker BH. Etanercept-induced subacute cutaneous lupus erythematosus. *Rheumatology (Oxford)*. 2001;40(11):1317-1319.
60. Lepore L, Marchetti F, Facchini S, Leone V, Ventura A. Drug-induced systemic lupus erythematosus associated with etanercept therapy in a child with juvenile idiopathic arthritis. *Clin Exp Rheumatol*. 2003;21(2):276-277.
61. Shakoor N, Michalska M, Harris CA, Block JA. Drug-induced systemic lupus erythematosus associated with etanercept therapy. *Lancet*. 2002;359(9306):579-580.
62. Hyrich KL, Silman AJ, Watson KD, Symmons DP. Anti-tumour necrosis factor alpha therapy in rheumatoid arthritis: an update on safety. *Ann Rheum Dis*. 2004;63(12):1538-1543.
63. Bloom BJ. Development of diabetes mellitus during etanercept therapy in a child with systemic-onset juvenile rheumatoid arthritis. *Arthritis Rheum*. 2000;43(11):2606-2608.
64. Allanore Y, Brémont C, Kahan A, Menkès CJ. Transient hyperthyroidism in a patient with rheumatoid arthritis treated by etanercept. *Clin Exp Rheumatol*. 2001;19(3):356-357.
65. Andrés E, Limbach FX, Goichot B, Sibilia J. Silent thyroiditis associated with etanercept in rheumatoid arthritis. *Ann Rheum Dis*. 2002;61(6):565.
66. Foeldvari I, Krüger E, Schneider T. Acute, non-obstructive, sterile cholecystitis associated with etanercept and infliximab for the treatment of juvenile polyarticular rheumatoid arthritis. *Ann Rheum Dis*. 2003;62(9):908-909.
67. Stern A, Riley R, Buckley L. Worsening of macrophage activation syndrome in a patient with adult onset Still's disease after initiation of etanercept therapy. *J Clin Rheumatol*. 2001;7(4):252-256.
68. Elwood RL, Pelszynski MM, Corman LI. Multifocal septic arthritis and osteomyelitis caused by group A *Streptococcus* in a patient receiving immunomodulating therapy with etanercept. *Pediatr Infect Dis J*. 2003;22(3):286-288.
69. Noguera-Pons R, Borrás-Blasco J, Romero-Crespo I, Antón-Torres R, Navarro-Ruiz A, González-Ferrandez JA. Optic neuritis with concurrent etanercept and isoniazid therapy. *Ann Pharmacother*. 2005;39(12):2131-2135.
70. Moreland LW, Baumgartner SW, Schiff MH, et al. Treatment of rheumatoid arthritis with a recombinant human tumor necrosis factor receptor (p75)-Fc fusion protein. *N Engl J Med*. 1997;337(3):141-147.
71. Smith D, Letendre S. Viral pneumonia as a serious complication of etanercept therapy. *Ann Intern Med*. 2002;136(2):174.
72. González-López MA, Blanco R, González-Vela MC, Fernández-Llaca H, Rodríguez-Valverde V. Development of sarcoidosis during etanercept therapy. *Arthritis Rheum*. 2006;55(5):817-820.
73. Verschueren K, Van Essche E, Verschueren P, Taelman V, Westhovens R. Development of sarcoidosis in etanercept-treated rheumatoid arthritis patients. *Clin Rheumatol*. 2007;26(11):1969-1971.

74. Baghai M, Osmon DR, Wolk DM, Wold LE, Haidukewych GJ, Matteson EL. Fatal sepsis in a patient with rheumatoid arthritis treated with etanercept. *Mayo Clin Proc.* 2001; 76(6):653-656.
75. Furst DE, Wallis R, Broder M, Beenhouwer DO. Tumor necrosis factor antagonists: different kinetics and/or mechanisms of action may explain differences in the risk for developing granulomatous infection. *Semin Arthritis Rheum.* 2006;36(3):159-167.
76. Chung ES, Packer M, Lo KH, Fasanmade AA, Willerson JT; Anti-TNF Therapy Against Congestive Heart Failure Investigators. Randomized, double-blind, placebo-controlled, pilot trial of infliximab, a chimeric monoclonal antibody to tumor necrosis factor- α , in patients with moderate-to-severe heart failure: results of the anti-TNF Therapy Against Congestive Heart Failure (ATTACH) trial. *Circulation.* 2003;107(25):3133-3140.
77. Bozkurt B, Torre-Amione G, Warren MS, et al. Results of targeted anti-tumor necrosis factor therapy with etanercept (ENBREL) in patients with advanced heart failure. *Circulation.* 2001;103(8):1044-1047.
78. Furst DE, Breedveld FC, Kalden JR, et al. Updated consensus statement on biological agents, specifically tumour necrosis factor α (TNF α) blocking agents and interleukin-1 receptor antagonist (IL-1ra), for the treatment of rheumatic diseases, 2005. *Ann Rheum Dis.* 2005; 64(suppl 4):iv2-iv14.
79. Brown SL, Greene MH, Gershon SK, Edwards ET, Braun MM. Tumor necrosis factor antagonist therapy and lymphoma development: twenty-six cases reported to the Food and Drug Administration. *Arthritis Rheum.* 2002; 46(12):3151-3158.
80. Wolfe F, Michaud K. Lymphoma in rheumatoid arthritis: the effect of methotrexate and anti-tumor necrosis factor therapy in 18,572 patients. *Arthritis Rheum.* 2004;50(6): 1740-1751.
81. Anderson PJ. Tumor necrosis factor inhibitors: clinical implications of their different immunogenicity profiles. *Semin Arthritis Rheum.* 2005;34(5)(suppl 1):19-22.
82. Weaver AL. Efficacy and safety of the anti-TNF biologic agents. *Mod Rheumatol.* 2004;14(2):101-112.
83. Baughman RP, Lower EE. Infliximab for refractory sarcoidosis. *Sarcoidosis Vasc Diffuse Lung Dis.* 2001;18(1):70-74.
84. Jatoi A, Sideras K, Nguyen PL. Tumor necrosis factor- α as a treatment target for the cancer anorexia/weight loss syndrome. *Support Cancer Ther.* 2004;1(4):237-242.
85. Doty JD, Mazur JE, Judson MA. Treatment of sarcoidosis with infliximab. *Chest.* 2005;127(3):1064-1071.
86. Baughman RP, Drent M, Kavuru M, et al; Sarcoidosis Investigators. Infliximab therapy in patients with chronic sarcoidosis and pulmonary involvement. *Am J Respir Crit Care Med.* 2006;174(7):795-802.
87. Rossman MD, Newman LS, Baughman RP, et al. A double-blinded, randomized, placebo-controlled trial of infliximab in subjects with active pulmonary sarcoidosis. *Sarcoidosis Vasc Diffuse Lung Dis.* 2006;23(3):201-208.
88. Antoniou KM, Mamoulaki M, Malagari K, et al. Infliximab therapy in pulmonary fibrosis associated with collagen vascular disease. *Clin Exp Rheumatol.* 2007;25(1):23-28.
89. Rennard SI, Fogarty C, Kelsen S, et al; COPD Investigators. The safety and efficacy of infliximab in moderate to severe chronic obstructive pulmonary disease. *Am J Respir Crit Care Med.* 2007;175(9):926-934.
90. Judson MA, Baughman RP, Costabel U, et al; Centocor T48 Sarcoidosis Investigators. Efficacy of infliximab in extrapulmonary sarcoidosis: results from a randomised trial. *Eur Respir J.* 2008;31(6):1189-1196.
91. van der Vaart H, Koëter GH, Postma DS, Kauffman HF, ten Hacken NH. First study of infliximab treatment in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med.* 2005;172(4):465-469.
92. Erin EM, Leaker BR, Nicholson GC, et al. The effects of a monoclonal antibody directed against tumor necrosis factor- α in asthma [published retraction appears in *Am J Respir Crit Care Med.* 2011;183(3):418]. *Am J Respir Crit Care Med.* 2006;174(7):753-762.
93. Yee AM, Pochapin MB. Treatment of complicated sarcoidosis with infliximab anti-tumor necrosis factor- α therapy. *Ann Intern Med.* 2001;135(1):27-31.
94. Pettersen JA, Zochodne DW, Bell RB, Martin L, Hill MD. Refractory neurosarcoidosis responding to infliximab. *Neurology.* 2002;59(10):1660-1661.
95. Katz JM, Bruno MK, Winterkorn JM, Nealon N. The pathogenesis and treatment of optic disc swelling in neurosarcoidosis: a unique therapeutic response to infliximab. *Arch Neurol.* 2003;60(3):426-430.
96. Meyerle JH, Shorr A. The use of infliximab in cutaneous sarcoidosis. *J Drugs Dermatol.* 2003;2(4):413-414.
97. Roberts SD, Wilkes DS, Burgett RA, Knox KS. Refractory sarcoidosis responding to infliximab. *Chest.* 2003;124(5): 2028-2031.
98. Ulbricht KU, Stoll M, Bierwirth J, Witte T, Schmidt RE. Successful tumor necrosis factor α blockade treatment in therapy-resistant sarcoidosis. *Arthritis Rheum.* 2003; 48(12):3542-3543.
99. Ali Y, Perlman E. Successful treatment of sarcoidosis. *Ann Intern Med.* 2004;140(11):W70.
100. Haley H, Cantrell W, Smith K. Infliximab therapy for sarcoidosis (lupus pernio). *Br J Dermatol.* 2004;150(1):146-149.
101. Jatoi A, Jett JR, Sloan J, et al. A pilot study on safety and pharmacokinetics of infliximab for the cancer anorexia/weight loss syndrome in non-small-cell lung cancer patients. *Support Care Cancer.* 2004;12(12):859-863.
102. Pritchard C, Nadarajah K. Tumour necrosis factor α inhibitor treatment for sarcoidosis refractory to conventional treatments: a report of five patients. *Ann Rheum Dis.* 2004;63(3):318-320.
103. Elliott MJ, Maini RN, Feldmann M, et al. Randomised double-blind comparison of chimeric monoclonal antibody to tumour necrosis factor α (cA2) versus placebo in rheumatoid arthritis. *Lancet.* 1994;344(8930):1105-1110.
104. Maini RN, Breedveld FC, Kalden JR, et al. Therapeutic efficacy of multiple intravenous infusions of anti-tumor necrosis factor α monoclonal antibody combined with low-dose weekly methotrexate in rheumatoid arthritis. *Arthritis Rheum.* 1998;41(9):1552-1563.
105. Maini R, St Clair EW, Breedveld F, et al; ATTRACT Study Group. Infliximab (chimeric anti-tumour necrosis factor α monoclonal antibody) versus placebo in rheumatoid arthritis patients receiving concomitant methotrexate: a randomised phase III trial. *Lancet.* 1999;354(9194): 1932-1939.
106. Present DH, Rutgeerts P, Targan S, et al. Infliximab for the treatment of fistulas in patients with Crohn's disease. *N Engl J Med.* 1999;340(18):1398-1405.
107. Lipsky PE, van der Heijde DM, St Clair EW, et al; Anti-Tumor Necrosis Factor Trial in Rheumatoid Arthritis with Concomitant Therapy Study Group. Infliximab and methotrexate in the treatment of rheumatoid arthritis. *N Engl J Med.* 2000;343(22):1594-1602.
108. Chaudhari U, Romano P, Mulcahy LD, Dooley LT, Baker DG, Gottlieb AB. Efficacy and safety of infliximab monotherapy for plaque-type psoriasis: a randomised trial. *Lancet.* 2001;357(9271):1842-1847.

109. Braun J, Brandt J, Listing J, et al. Treatment of active ankylosing spondylitis with infliximab: a randomised controlled multicentre trial. *Lancet*. 2002;359(9313):1187-1193.
110. Hanauer SB, Feagan BG, Lichtenstein GR, et al; ACCENT I Study Group. Maintenance infliximab for Crohn's disease: the ACCENT I randomised trial. *Lancet*. 2002;359(9317):1541-1549.
111. Van Den Bosch F, Kruithof E, Baeten D, et al. Randomized double-blind comparison of chimeric monoclonal antibody to tumor necrosis factor alpha (infliximab) versus placebo in active spondylarthropathy. *Arthritis Rheum*. 2002;46(3):755-765.
112. Booth A, Harper L, Hammad T, et al. Prospective study of TNFalpha blockade with infliximab in anti-neutrophil cytoplasmic antibody-associated systemic vasculitis. *J Am Soc Nephrol*. 2004;15(3):717-721.
113. Durez P, Nzeuseu Toukap A, Lauwerys BR, et al. A randomised comparative study of the short term clinical and biological effects of intravenous pulse methylprednisolone and infliximab in patients with active rheumatoid arthritis despite methotrexate treatment. *Ann Rheum Dis*. 2004;63(9):1069-1074.
114. Mariette X, Ravaud P, Steinfeld S, et al. Inefficacy of infliximab in primary Sjögren's syndrome: results of the randomized, controlled Trial of Remicade in Primary Sjögren's Syndrome (TRIPSS). *Arthritis Rheum*. 2004;50(4):1270-1276.
115. Sands BE, Anderson FH, Bernstein CN, et al. Infliximab maintenance therapy for fistulizing Crohn's disease. *N Engl J Med*. 2004;350(9):876-885.
116. St Clair EW, van der Heijde DM, Smolen JS, et al; Active-Controlled Study of Patients Receiving Infliximab for the Treatment of Rheumatoid Arthritis of Early Onset Study Group. Combination of infliximab and methotrexate therapy for early rheumatoid arthritis: a randomized, controlled trial. *Arthritis Rheum*. 2004;50(11):3432-3443.
117. Abe T. [Lesson from ACR guidelines for management of RA]. *Nihon Rinsho*. 2005;63(suppl 1):431-438.
118. Braun J, Baraliakos X, Brandt J, et al. Persistent clinical response to the anti-TNF-alpha antibody infliximab in patients with ankylosing spondylitis over 3 years. *Rheumatology (Oxford)*. 2005;44(5):670-676.
119. Korhonen T, Karppinen J, Paimela L, et al. The treatment of disc herniation-induced sciatica with infliximab: results of a randomized, controlled, 3-month follow-up study. *Spine*. 2005;30(24):2724-2728.
120. Marzo-Ortega H, McGonagle D, Jarrett S, et al. Infliximab in combination with methotrexate in active ankylosing spondylitis: a clinical and imaging study. *Ann Rheum Dis*. 2005;64(11):1568-1575.
121. Reich K, Nestle FO, Papp K, et al; EXPRESS study investigators. Infliximab induction and maintenance therapy for moderate-to-severe psoriasis: a phase III, multicentre, double-blind trial. *Lancet*. 2005;366(9494):1367-1374.
122. Rutgeerts P, Sandborn WJ, Feagan BG, et al. Infliximab for induction and maintenance therapy for ulcerative colitis. *N Engl J Med*. 2005;353(23):2462-2476.
123. van der Heijde D, Dijkman B, Geusens P, et al; Ankylosing Spondylitis Study for the Evaluation of Recombinant Infliximab Therapy Study Group. Efficacy and safety of infliximab in patients with ankylosing spondylitis: results of a randomized, placebo-controlled trial (ASSERT). *Arthritis Rheum*. 2005;52(2):582-591.
124. Abe T, Takeuchi T, Miyasaka N, et al. A multicenter, double-blind, randomized, placebo controlled trial of infliximab combined with low dose methotrexate in Japanese patients with rheumatoid arthritis. *J Rheumatol*. 2006;33(1):37-44.
125. Allaart CF, Goekoop-Ruiterman YP, de Vries-Bouwstra JK, Breedveld FC, Dijkman BA; FARR study group. Aiming at low disease activity in rheumatoid arthritis with initial combination therapy or initial monotherapy strategies: the BeSt study. *Clin Exp Rheumatol*. 2006;24(6)(suppl 43):S-77-S-82.
126. Braun J, Landewé R, Hermann KG, et al; ASSERT Study Group. Major reduction in spinal inflammation in patients with ankylosing spondylitis after treatment with infliximab: results of a multicenter, randomized, double-blind, placebo-controlled magnetic resonance imaging study. *Arthritis Rheum*. 2006;54(5):1646-1652.
127. Lémann M, Mary JY, Duclos B, et al; Groupe d'Etude Thérapeutique des Affections Inflammatoires du Tube Digestif (GETAID). Infliximab plus azathioprine for steroid-dependent Crohn's disease patients: a randomized placebo-controlled trial. *Gastroenterology*. 2006;130(4):1054-1061.
128. Taylor PC, Steuer A, Gruber J, et al. Ultrasonographic and radiographic results from a two-year controlled trial of immediate or one-year-delayed addition of infliximab to ongoing methotrexate therapy in patients with erosive early rheumatoid arthritis. *Arthritis Rheum*. 2006;54(1):47-53.
129. Westhovens R, Yocum D, Han J, et al; START Study Group. The safety of infliximab, combined with background treatments, among patients with rheumatoid arthritis and various comorbidities: a large, randomized, placebo-controlled trial [published correction appears in *Arthritis Rheum*. 2007;56(5):1675]. *Arthritis Rheum*. 2006;54(4):1075-1086.
130. Goekoop-Ruiterman YP, de Vries-Bouwstra JK, Allaart CF, et al. Comparison of treatment strategies in early rheumatoid arthritis: a randomized trial. *Ann Intern Med*. 2007;146(6):406-415.
131. Hoffman GS, Cid MC, Rendt-Zagar KE, et al; Infliximab-GCA Study Group. Infliximab for maintenance of glucocorticosteroid-induced remission of giant cell arteritis: a randomized trial. *Ann Intern Med*. 2007;146(9):621-630.
132. Kavanaugh A, Krueger GG, Beutler A, et al; IMPACT 2 Study Group. Infliximab maintains a high degree of clinical response in patients with active psoriatic arthritis through 1 year of treatment: results from the IMPACT 2 trial. *Ann Rheum Dis*. 2007;66(4):498-505.
133. Salvarani C, Macchioni P, Manzini C, et al. Infliximab plus prednisone or placebo plus prednisone for the initial treatment of polymyalgia rheumatica: a randomized trial. *Ann Intern Med*. 2007;146(9):631-639.
134. Serio B, Paolino S, Ferrone C, Cutolo M. Effects of etanercept or infliximab treatment on lipid profile and insulin resistance in patients with refractory rheumatoid arthritis. *Clin Rheumatol*. 2007;26(10):1799-1800.
135. Dahlqvist SR, Engstrand S, Berglin E, Johnson O. Conversion towards an atherogenic lipid profile in rheumatoid arthritis patients during long-term infliximab therapy. *Scand J Rheumatol*. 2006;35(2):107-111.
136. Strangfeld A, Listing J. Infection and musculoskeletal conditions: bacterial and opportunistic infections during anti-TNF therapy. *Best Pract Res Clin Rheumatol*. 2006;20(6):1181-1195.
137. Ledingham J, Deighton C; British Society for Rheumatology Standards, Guidelines and Audit Working Group. Update on the British Society for Rheumatology guidelines for prescribing TNFalpha blockers in adults with rheumatoid arthritis (update of previous guidelines of April 2001). *Rheumatology (Oxford)*. 2005;44(2):157-163.
138. CDC. Tuberculosis associated with blocking agents against tumor necrosis factor- α . *Morb Mortal Wkly Rep*. 2004;53(30):683-686.

139. Winthrop KL, Siegel JN, Jereb J, Taylor Z, Iademarco MF. Tuberculosis associated with therapy against tumor necrosis factor alpha. *Arthritis Rheum.* 2005;52(10):2968-2974.
140. Gómez-Reino JJ, Carmona L, Valverde VR, Mola EM, Montero MD; BIOBADASER Group. Treatment of rheumatoid arthritis with tumor necrosis factor inhibitors may predispose to significant increase in tuberculosis risk: a multi-center active-surveillance report. *Arthritis Rheum.* 2003;48(8):2122-2127.
141. Gardam MA, Keystone EC, Menzies R, et al. Anti-tumour necrosis factor agents and tuberculosis risk: mechanisms of action and clinical management. *Lancet Infect Dis.* 2003;3(3):148-155.
142. Mohan N, Edwards ET, Cupps TR, et al. Demyelination occurring during anti-tumor necrosis factor alpha therapy for inflammatory arthritides. *Arthritis Rheum.* 2001;44(12):2862-2869.
143. Allanore Y, Kahan A, Sellam J, Ekindjian OG, Borderie D. Effects of repeated infliximab therapy on serum lipid profile in patients with refractory rheumatoid arthritis. *Clin Chim Acta.* 2006;365(1-2):143-148.
144. Kiortsis DN, Mavridis AK, Filippatos TD, Vasakos S, Nikas SN, Drosos AA. Effects of infliximab treatment on lipoprotein profile in patients with rheumatoid arthritis and ankylosing spondylitis. *J Rheumatol.* 2006;33(5):921-923.
145. Peters MJ, Vis M, van Halm VP, et al. Changes in lipid profile during infliximab and corticosteroid treatment in rheumatoid arthritis. *Ann Rheum Dis.* 2007;66(7):958-961.
146. Vis M, Nurmohamed MT, Wolbink G, et al. Short term effects of infliximab on the lipid profile in patients with rheumatoid arthritis. *J Rheumatol.* 2005;32(2):252-255.
147. Popa C, van den Hoogen FH, Radstake TR, et al. Modulation of lipoprotein plasma concentrations during long-term anti-TNF therapy in patients with active rheumatoid arthritis. *Ann Rheum Dis.* 2007;66(11):1503-1507.
148. REMICADE IV injection, infliximab IV injection [package insert]. Malvern, PA: Centocor, Inc; 2006.
149. Carmona L, Gómez-Reino JJ, Rodríguez-Valverde V, et al; BIOBADASER Group. Effectiveness of recommendations to prevent reactivation of latent tuberculosis infection in patients treated with tumor necrosis factor antagonists. *Arthritis Rheum.* 2005;52(6):1766-1772.
150. Gómez-Reino JJ, Carmona L, Angel Descalzo M; BIOBADASER Group. Risk of tuberculosis in patients treated with tumor necrosis factor antagonists due to incomplete prevention of reactivation of latent infection. *Arthritis Rheum.* 2007;57(5):756-761.
151. Keenan RJ, Konishi H, Kawai A, et al. Clinical trial of tacrolimus versus cyclosporine in lung transplantation. *Ann Thorac Surg.* 1995;60(3):580-584.
152. Zuckermann A, Reichenspurner H, Birsan T, et al. Cyclosporine A versus tacrolimus in combination with mycophenolate mofetil and steroids as primary immunosuppression after lung transplantation: one-year results of a 2-center prospective randomized trial. *J Thorac Cardiovasc Surg.* 2003;125(4):891-900.
153. Date H. Experience with cyclosporine in living-donor lobar lung transplantation. *Transplant Proc.* 2004;36(suppl 2):S349-S351.
154. Wyser CP, van Schalkwyk EM, Alheit B, Bardin PG, Joubert JR. Treatment of progressive pulmonary sarcoidosis with cyclosporin A. A randomized controlled trial. *Am J Respir Crit Care Med.* 1997;156(5):1371-1376.
155. Venuta F, Rendina EA, Ciriaco P, et al. Efficacy of cyclosporine to reduce steroids in patients with idiopathic pulmonary fibrosis before lung transplantation. *J Heart Lung Transplant.* 1993;12(6 pt 1):909-914.
156. Iacono AT, Smaldone GC, Keenan RJ, et al. Dose-related reversal of acute lung rejection by aerosolized cyclosporine. *Am J Respir Crit Care Med.* 1997;155(5):1690-1698.
157. Iacono AT, Corcoran TE, Griffith BP, et al. Aerosol cyclosporin therapy in lung transplant recipients with bronchiolitis obliterans. *Eur Respir J.* 2004;23(3):384-390.
158. Iacono AT, Johnson BA, Grgurich WF, et al. A randomized trial of inhaled cyclosporine in lung-transplant recipients. *N Engl J Med.* 2006;354(2):141-150.
159. Devineni R, McKenzie N, Keown P, Kostuk W, Stiller C, Silver M. Cyclosporine in cardiac transplantation. *Can J Surg.* 1984;27(3):252-254.
160. Griffiths MH, Crowe AV, Papadaki L, et al. Cyclosporin nephrotoxicity in heart and lung transplant patients. *QJM.* 1996;89(10):751-763.
161. Kilpatrick NM, Weintraub RG, Lucas JO, Shipp A, Byrt T, Wilkinson JL. Gingival overgrowth in pediatric heart and heart-lung transplant recipients. *J Heart Lung Transplant.* 1997;16(12):1231-1237.
162. Mikhail G, Eadon H, Leaver N, et al. An investigation of the pharmacokinetics, toxicity, and clinical efficacy of Neoral cyclosporin in cystic fibrosis patients. *Transplant Proc.* 1997;29(1-2):599-601.
163. Trull A, Steel L, Sharples L, et al. Randomized, trough blood cyclosporine concentration-controlled trial to compare the pharmacodynamics of Sandimmune and Neoral in de novo lung transplant recipients. *Ther Drug Monit.* 1999;21(1):17-26.
164. Tsimaratos M, Viard L, Kreitmann B, et al. Kidney function in cyclosporine-treated paediatric pulmonary transplant recipients. *Transplantation.* 2000;69(10):2055-2059.
165. Glanville AR, Morton JM, Aboyoun CL, Plit ML, Malouf MA. Cyclosporine C2 monitoring improves renal dysfunction after lung transplantation. *J Heart Lung Transplant.* 2004;23(10):1170-1174.
166. Thomason JM, Seymour RA, Ellis JS. Risk factors for gingival overgrowth in patients medicated with cyclosporin in the absence of calcium channel blockers. *J Clin Periodontol.* 2005;32(3):273-279.
167. Shennib H, Massard G, Gauthier R, Colman N, Mulder D. Single lung transplantation for cystic fibrosis: is it an option? Cystic Fibrosis Transplant Study Group. *J Heart Lung Transplant.* 1993;12(2):288-293.
168. Knoop C, Vervier I, Thiry P, et al. Cyclosporine pharmacokinetics and dose monitoring after lung transplantation: comparison between cystic fibrosis and other conditions. *Transplantation.* 2003;76(4):683-688.
169. Morton JM, Aboyoun CL, Malouf MA, Plit ML, Glanville AR. Enhanced clinical utility of de novo cyclosporine C2 monitoring after lung transplantation. *J Heart Lung Transplant.* 2004;23(9):1035-1039.
170. Jaksch P, Kocher A, Neuhauser P, et al. Monitoring C2 level predicts exposure in maintenance lung transplant patients receiving the microemulsion formulation of cyclosporine (Neoral). *J Heart Lung Transplant.* 2005;24(8):1076-1080.
171. Shennib H, Auger JL. Diltiazem improves cyclosporine dosage in cystic fibrosis lung transplant recipients. *J Heart Lung Transplant.* 1994;13(2):292-296.
172. Trull AK, Best NG, Tan KK, et al. Blood cyclosporin concentrations but not doses correlate with acute changes in renal function following heart and heart-lung transplantation. *Ther Drug Monit.* 1992;14(4):275-280.
173. Banner NR, Yacoub MH. Cyclosporine in thoracic organ transplantation. *Transplant Proc.* 2004;36(suppl 2):S302-S308.
174. Kapturczak MH, Meier-Kriesche HU, Kaplan B. Pharmacology of calcineurin antagonists. *Transplant Proc.* 2004;36(suppl 2):S25-S32.

175. NEORAL soft gelatin oral capsules, oral solution, cyclosporine soft gelatin capsules, oral solution [package insert]. East Hanover, NJ: Novartis Pharmaceuticals; 2006.
176. Rayes N, Neuhaus R, David M, Steinmüller T, Bechstein WO, Neuhaus P. Pregnancies following liver transplantation—how safe are they? A report of 19 cases under cyclosporine A and tacrolimus. *Clin Transplant*. 1998;12(5):396-400.
177. Wu A, Nashan B, Messner U, et al. Outcome of 22 successful pregnancies after liver transplantation. *Clin Transplant*. 1998;12(5):454-464.
178. Celik MR, Lederer DJ, Wilt J, et al. Tacrolimus and azathioprine versus cyclosporine and mycophenolate mofetil after lung transplantation: a retrospective cohort study. *J Heart Lung Transplant*. 2009;28(7):697-703.
179. Griffith BP, Bando K, Hardesty RL, et al. A prospective randomized trial of FK506 versus cyclosporine after human pulmonary transplantation. *Transplantation*. 1994;57(6):848-851.
180. Kesten S, Chaparro C, Scavuzzo M, Gutierrez C. Tacrolimus as rescue therapy for bronchiolitis obliterans syndrome. *J Heart Lung Transplant*. 1997;16(9):905-912.
181. Ross DJ, Lewis MI, Kramer M, Vo A, Kass RM. FK 506 'rescue' immunosuppression for obliterative bronchiolitis after lung transplantation. *Chest*. 1997;112(5):1175-1179.
182. Mentzer RM Jr, Jahania MS, Lasley RD. Tacrolimus as a rescue immunosuppressant after heart and lung transplantation. The U.S. Multicenter FK506 Study Group. *Transplantation*. 1998;65(1):109-113.
183. Wiebe K, Harringer W, Franke U, et al. FK506 rescue therapy in lung transplantation. *Transplant Proc*. 1998;30(4):1508-1509.
184. Onsager DR, Canver CC, Jahania MS, et al. Efficacy of tacrolimus in the treatment of refractory rejection in heart and lung transplant recipients. *J Heart Lung Transplant*. 1999;18(5):448-455.
185. Reichenspurner H, Kur F, Treede H, et al. Optimization of the immunosuppressive protocol after lung transplantation. *Transplantation*. 1999;68(1):67-71.
186. Treede H, Klepetko W, Reichenspurner H, et al; Munich and Vienna Lung Transplant Group. Tacrolimus versus cyclosporine after lung transplantation: a prospective, open, randomized two-center trial comparing two different immunosuppressive protocols. *J Heart Lung Transplant*. 2001;20(5):511-517.
187. Sarahrudi K, Carretta A, Wisser W, et al. The value of switching from cyclosporine to tacrolimus in the treatment of refractory acute rejection and obliterative bronchiolitis after lung transplantation. *Transpl Int*. 2002;15(1):24-28.
188. Heisel O, Heisel R, Balshaw R, Keown P. New onset diabetes mellitus in patients receiving calcineurin inhibitors: a systematic review and meta-analysis. *Am J Transplant*. 2004;4(4):583-595.
189. Sarahrudi K, Estenne M, Corris P, et al. International experience with conversion from cyclosporine to tacrolimus for acute and chronic lung allograft rejection. *J Thorac Cardiovasc Surg*. 2004;127(4):1126-1132.
190. Knoop C, Thiry P, Saint-Marcoux F, Rousseau A, Marquet P, Estenne M. Tacrolimus pharmacokinetics and dose monitoring after lung transplantation for cystic fibrosis and other conditions. *Am J Transplant*. 2005;5(6):1477-1482.
191. Barten MJ, Rahmel A, Garbade J, et al. Pharmacodynamic monitoring of the conversion of cyclosporine to tacrolimus in heart and lung transplant recipients. *Transplant Proc*. 2005;37(10):4532-4534.
192. Faivre L, Saoudi S, Astier A, et al. FK 506 dose in transplantation: from theory to practice. *Transplant Proc*. 2001;33(4):2594-2597.
193. Prograf, tacrolimus [package insert]. Deerfield, IL: Fujisawa Healthcare, Inc; 2004.
194. Duncan MD, Wilkes DS. Transplant-related immunosuppression: a review of immunosuppression and pulmonary infections. *Proc Am Thorac Soc*. 2005;2(5):449-455.
195. Christians U, Jacobsen W, Benet LZ, Lampen A. Mechanisms of clinically relevant drug interactions associated with tacrolimus. *Clin Pharmacokinet*. 2002;41(11):813-851.
196. van Gelder T. Drug interactions with tacrolimus. *Drug Saf*. 2002;25(10):707-712.
197. Jain A, Venkataramanan R, Fung JJ, et al. Pregnancy after liver transplantation under tacrolimus. *Transplantation*. 1997;64(4):559-565.
198. Alak AM. Measurement of tacrolimus (FK506) and its metabolites: a review of assay development and application in therapeutic drug monitoring and pharmacokinetic studies. *Ther Drug Monit*. 1997;19(3):338-351.
199. Magliocca JF, Knechtle SJ. The evolving role of alemtuzumab (Campath-1H) for immunosuppressive therapy in organ transplantation. *Transpl Int*. 2006;19(9):705-714.
200. Pangalis GA, Dimopoulou MN, Angelopoulou MK, et al. Campath-1H (anti-CD52) monoclonal antibody therapy in lymphoproliferative disorders. *Med Oncol*. 2001;18(2):99-107.
201. Reams BD, Musselwhite LW, Zaas DW, et al. Alemtuzumab in the treatment of refractory acute rejection and bronchiolitis obliterans syndrome after human lung transplantation. *Am J Transplant*. 2007;7(12):2802-2808.
202. Knechtle SJ, Fernandez LA, Pirsch JD, et al. Campath-1H in renal transplantation: the University of Wisconsin experience. *Surgery*. 2004;136(4):754-760.
203. Ciancio G, Burke GW, Gaynor JJ, et al. A randomized trial of three renal transplant induction antibodies: early comparison of tacrolimus, mycophenolate mofetil, and steroid dosing, and newer immune-monitoring. *Transplantation*. 2005;80(4):457-465.
204. Vathsala A, Ona ET, Tan SY, et al. Randomized trial of alemtuzumab for prevention of graft rejection and preservation of renal function after kidney transplantation. *Transplantation*. 2005;80(6):765-774.
205. CAMPATH (Alemtuzumab) [package insert]. San Antonio, TX: ILEX Pharmaceuticals, LP; 2005.
206. Kirk AD, Hale DA, Swanson SJ, Mannon RB. Autoimmune thyroid disease after renal transplantation using depletion induction with alemtuzumab. *Am J Transplant*. 2006;6(5 pt 1):1084-1085.
207. McCurry KR, Iacono A, Zeevi A, et al. Early outcomes in human lung transplantation with Thymoglobulin or Campath-1H for recipient pretreatment followed by post-transplant tacrolimus near-monotherapy. *J Thorac Cardiovasc Surg*. 2005;130(2):528-537.
208. Watson CJ, Bradley JA, Friend PJ, et al. Alemtuzumab (CAMPATH 1H) induction therapy in cadaveric kidney transplantation—efficacy and safety at five years. *Am J Transplant*. 2005;5(6):1347-1353.
209. Peleg AY, Husain S, Kwak EJ, et al. Opportunistic infections in 547 organ transplant recipients receiving alemtuzumab, a humanized monoclonal CD-52 antibody. *Clin Infect Dis*. 2007;44(2):204-212.
210. Palmer SM, Miralles AP, Lawrence CM, Gaynor JW, Davis RD, Tapson VF. Rabbit antithymocyte globulin decreases acute rejection after lung transplantation: results of a randomized, prospective study. *Chest*. 1999;116(1):127-133.
211. Krasinskas AM, Kreisel D, Acker MA, et al. CD3 monitoring of antithymocyte globulin therapy in thoracic organ transplantation. *Transplantation*. 2002;73(8):1339-1341.

212. Mullen JC, Oreopoulos A, Lien DC, et al. A randomized, controlled trial of daclizumab vs anti-thymocyte globulin induction for lung transplantation. *J Heart Lung Transplant*. 2007;26(5):504-510.
213. Souillou JP, Cantarovich D, Le Mauff B, et al. Randomized controlled trial of a monoclonal antibody against the interleukin-2 receptor (3B3.1) as compared with rabbit antithymocyte globulin for prophylaxis against rejection of renal allografts. *N Engl J Med*. 1990;322(17):1175-1182.
214. ATGAM IV injection, lymphocyte immune globulin, anti-thymocyte globulin [equine] sterile IV injection [package insert]. Kalamazoo, MI: Pharmacia & Upjohn Company; 2005.
215. Hourmant M, Bedrossian J, Durand D, et al. A randomized multicenter trial comparing leukocyte function-associated antigen-1 monoclonal antibody with rabbit antithymocyte globulin as induction treatment in first kidney transplantations. *Transplantation*. 1996;62(11):1565-1570.
216. Wain JC, Wright CD, Ryan DP, Zorb SL, Mathisen DJ, Ginns LC. Induction immunosuppression for lung transplantation with OKT3. *Ann Thorac Surg*. 1999;67(1):187-193.
217. Barlow CW, Moon MR, Green GR, et al. Rabbit antithymocyte globulin versus OKT3 induction therapy after heart-lung and lung transplantation: effect on survival, rejection, infection, and obliterative bronchiolitis. *Transpl Int*. 2001;14(4):234-239.
218. Brock MV, Borja MC, Ferber L, et al. Induction therapy in lung transplantation: a prospective, controlled clinical trial comparing OKT3, anti-thymocyte globulin, and daclizumab. *J Heart Lung Transplant*. 2001;20(12):1282-1290.
219. Boland GJ, Hene RJ, Ververs C, de Haan MA, de Gast GC. Factors influencing the occurrence of active cytomegalovirus (CMV) infections after organ transplantation. *Clin Exp Immunol*. 1993;94(2):306-312.
220. Portela D, Patel R, Larson-Keller JJ, et al. OKT3 treatment for allograft rejection is a risk factor for cytomegalovirus disease in liver transplantation. *J Infect Dis*. 1995;171(4):1014-1018.
221. Keay S, Oldach D, Wiland A, et al. Posttransplantation lymphoproliferative disorder associated with OKT3 and decreased antiviral prophylaxis in pancreas transplant recipients. *Clin Infect Dis*. 1998;26(3):596-600.
222. Orthoclone OKT3 [package insert]. Raritan, NJ: Ortho Biotech; 1999.
223. Parnham AP, Low A, Finch P, Perlman D, Thomas MA. Recurrent graft pain following renal autotransplantation for loin pain haematuria syndrome. *Br J Urol*. 1996;78(1):25-28.
224. Möse JR. Effect of echinacin on phagocytosis and natural killer cells [in German]. *Med Welt*. 1983;34(51-52):1463-1467.
225. Melchart D, Linde K, Worku F, et al. Results of five randomized studies on the immunomodulatory activity of preparations of *Echinacea*. *J Altern Complement Med*. 1995;1(2):145-160.
226. Wagner H, Jurcic K. Immunological studies of Revitonil, a phytopharmaceutical containing *Echinacea purpurea* and *Glycyrrhiza glabra* root extract. *Phytomedicine*. 2002;9(5):390-397.
227. Avivi I, Robinson S, Goldstone A. Clinical use of rituximab in haematological malignancies. *Br J Cancer*. 2003;89(8):1389-1394.
228. Balfour IC, Fiore A, Graff RJ, Knutsen AP. Use of rituximab to decrease panel-reactive antibodies. *J Heart Lung Transplant*. 2005;24(5):628-630.
229. Pescovitz MD. The use of rituximab, anti-CD20 monoclonal antibody, in pediatric transplantation. *Pediatr Transplant*. 2004;8(1):9-21.
230. Blaes AH, Peterson BA, Bartlett N, Dunn DL, Morrison VA. Rituximab therapy is effective for posttransplant lymphoproliferative disorders after solid organ transplantation: results of a phase II trial. *Cancer*. 2005;104(8):1661-1667.
231. Choquet S, Leblond V, Herbrecht R, et al. Efficacy and safety of rituximab in B-cell post-transplantation lymphoproliferative disorders: results of a prospective multicenter phase 2 study. *Blood*. 2006;107(8):3053-3057.
232. Cook RC, Connors JM, Gascoyne RD, Fradet G, Levy RD. Treatment of post-transplant lymphoproliferative disease with rituximab monoclonal antibody after lung transplantation. *Lancet*. 1999;354(9191):1698-1699.
233. Milpied N, Vasseur B, Parquet N, et al. Humanized anti-CD20 monoclonal antibody (Rituximab) in post transplant B-lymphoproliferative disorder: a retrospective analysis on 32 patients. *Ann Oncol*. 2000;11(suppl 1):113-116.
234. Reams BD, McAdams HP, Howell DN, Steele MP, Davis RD, Palmer SM. Posttransplant lymphoproliferative disorder: incidence, presentation, and response to treatment in lung transplant recipients. *Chest*. 2003;124(4):1242-1249.
235. Verschuuren EA, Stevens SJ, van Imhoff GW, et al. Treatment of posttransplant lymphoproliferative disease with rituximab: the remission, the relapse, and the complication. *Transplantation*. 2002;73(1):100-104.
236. Oertel SH, Verschuuren E, Reinke P, et al. Effect of anti-CD 20 antibody rituximab in patients with post-transplant lymphoproliferative disorder (PTLD). *Am J Transplant*. 2005;5(12):2901-2906.
237. Rituxan (Rituximab) [package insert]. Weston, MA: Biogen Idec Inc and Genentech Inc; 2006.
238. van der Kolk LE, Baars JW, Prins MH, van Oers MH. Rituximab treatment results in impaired secondary humoral immune responsiveness. *Blood*. 2002;100(6):2257-2259.
239. FDA MedWatch. *Information for Healthcare Professionals. Rituximab (marketed as Rituxan)*. Rockville, MD: Food and Drug Administration; 2006.
240. Bennett CM, Rogers ZR, Kinnamon DD, et al. Prospective phase 1/2 study of rituximab in childhood and adolescent chronic immune thrombocytopenic purpura. *Blood*. 2006;107(7):2639-2642.
241. D'Arcy CA, Mannik M. Serum sickness secondary to treatment with the murine-human chimeric antibody IDEC-C2B8 (rituximab). *Arthritis Rheum*. 2001;44(7):1717-1718.
242. Hellerstedt B, Ahmed A. Delayed-type hypersensitivity reaction or serum sickness after rituximab treatment. *Ann Oncol*. 2003;14(12):1792.
243. Herishanu Y. Rituximab-induced serum sickness. *Am J Hematol*. 2002;70(4):329.
244. Wang J, Wiley JM, Luddy R, Greenberg J, Feuerstein MA, Bussell JB. Chronic immune thrombocytopenic purpura in children: assessment of rituximab treatment. *J Pediatr*. 2005;146(2):217-221.
245. Burton C, Kaczmarek R, Jan-Mohamed R. Interstitial pneumonitis related to rituximab therapy. *N Engl J Med*. 2003;348(26):2690-2691.
246. Herishanu Y, Polliack A, Leider-Trejo L, Grieff Y, Metser U, Naparstek E. Fatal interstitial pneumonitis related to rituximab-containing regimen. *Clin Lymphoma Myeloma*. 2006;6(5):407-409.
247. Lee Y, Kyung SY, Choi SJ, et al. Two cases of interstitial pneumonitis caused by rituximab therapy. *Korean J Intern Med*. 2006;21(3):183-186.
248. Aksoy S, Dizdar O, Hayran M, Harputluo lu H. Infectious complications of rituximab in patients with lymphoma during maintenance therapy: a systematic review and meta-analysis. *Leuk Lymphoma*. 2009;50(3):357-365.

249. Kimby E. Tolerability and safety of rituximab (MabThera). *Cancer Treat Rev.* 2005;31(6):456-473.
250. Friedrichs B, Tiemann M, Salwender H, Verpoort K, Wenger MK, Schmitz N. The effects of rituximab treatment during pregnancy on a neonate. *Haematologica.* 2006; 91(10):1426-1427.
251. Trulock EP, Edwards LB, Taylor DO, Boucek MM, Keck BM, Hertz MI; International Society for Heart and Lung Transplantation. Registry of the International Society for Heart and Lung Transplantation: twenty-third official adult lung and heart-lung transplantation report—2006. *J Heart Lung Transplant.* 2006;25(8):880-892.
252. Nashan B, Moore P, Amlot P, Schmidt AG, Abeywickrama K, Souillou JP; CHIB 201 International Study Group. Randomised trial of basiliximab versus placebo for control of acute cellular rejection in renal allograft recipients. *Lancet.* 1997;350(9086):1193-1198.
253. Kahan BD, Rajagopalan PR, Hall M; United States Simulect Renal Study Group. Reduction of the occurrence of acute cellular rejection among renal allograft recipients treated with basiliximab, a chimeric anti-interleukin-2-receptor monoclonal antibody. *Transplantation.* 1999;67(2):276-284.
254. Lebranchu Y, Bridoux F, Büchler M, et al. Immunoprophylaxis with basiliximab compared with antithymocyte globulin in renal transplant patients receiving MMF-containing triple therapy. *Am J Transplant.* 2002;2(1):48-56.
255. Neuhaus P, Clavien PA, Kittur D, et al; CHIC 304 International Liver Study Group. Improved treatment response with basiliximab immunoprophylaxis after liver transplantation: results from a double-blind randomized placebo-controlled trial. *Liver Transpl.* 2002;8(2):132-142.
256. Matl I, Bachleda P, Lao M, et al. Safety and efficacy of an alternative basiliximab (Simulect) regimen after renal transplantation: administration of a single 40-mg dose on the first postoperative day in patients receiving triple therapy with azathioprine. *Transpl Int.* 2003;16(1):45-52.
257. Mourad G, Rostaing L, Legendre C, Garrigue V, Thervet E, Durand D. Sequential protocols using basiliximab versus antithymocyte globulins in renal-transplant patients receiving mycophenolate mofetil and steroids. *Transplantation.* 2004;78(4):584-590.
258. Pageaux GP, Calmus Y, Boillot O, et al; French CHI-F-01 Study Group. Steroid withdrawal at day 14 after liver transplantation: a double-blind, placebo-controlled study. *Liver Transpl.* 2004;10(12):1454-1460.
259. Mehra MR, Zucker MJ, Wagoner L, et al. A multicenter, prospective, randomized, double-blind trial of basiliximab in heart transplantation. *J Heart Lung Transplant.* 2005; 24(9):1297-1304.
260. Vítko S, Klinger M, Salmela K, et al. Two corticosteroid-free regimens-tacrolimus monotherapy after basiliximab administration and tacrolimus/mycophenolate mofetil-in comparison with a standard triple regimen in renal transplantation: results of the Atlas study. *Transplantation.* 2005; 80(12):1734-1741.
261. Grenda R, Watson A, Vondrak K, et al. A prospective, randomized, multicenter trial of tacrolimus-based therapy with or without basiliximab in pediatric renal transplantation. *Am J Transplant.* 2006;6(7):1666-1672.
262. Segovia J, Rodríguez-Lambert JL, Crespo-Leiro MG, et al. A randomized multicenter comparison of basiliximab and muromonab (OKT3) in heart transplantation: SIMCOR study. *Transplantation.* 2006;81(11):1542-1548.
263. Spada M, Petz W, Bertani A, et al. Randomized trial of basiliximab induction versus steroid therapy in pediatric liver allograft recipients under tacrolimus immunosuppression. *Am J Transplant.* 2006;6(8):1913-1921.
264. Kahan BD, Wong RL, Carter C, et al. A phase I study of a 4-week course of SDZ-RAD (RAD) quiescent cyclosporine-prednisone-treated renal transplant recipients. *Transplantation.* 1999;68(8):1100-1106.
265. Borro JM, De la Torre M, Míguélez C, Fernandez R, Gonzalez D, Lemos C. Comparative study of basiliximab treatment in lung transplantation. *Transplant Proc.* 2005;37(9):3996-3998.
266. Hachem RR, Chakinala MM, Yusen RD, et al. A comparison of basiliximab and anti-thymocyte globulin as induction agents after lung transplantation. *J Heart Lung Transplant.* 2005;24(9):1320-1326.
267. Sollinger H, Kaplan B, Pescovitz MD, et al. Basiliximab versus antithymocyte globulin for prevention of acute renal allograft rejection. *Transplantation.* 2001;72(12):1915-1919.
268. Lawen JG, Davies EA, Mourad G, et al; Simulect International Study Group. Randomized double-blind study of immunoprophylaxis with basiliximab, a chimeric anti-interleukin-2 receptor monoclonal antibody, in combination with mycophenolate mofetil-containing triple therapy in renal transplantation. *Transplantation.* 2003;75(1):37-43.
269. Filippini F, Callea F, Salizzoni M, et al. Double-blind comparison of hepatitis C histological recurrence rate in HCV+ liver transplant recipients given basiliximab + steroids or basiliximab + placebo, in addition to cyclosporine and azathioprine. *Transplantation.* 2004;78(10):1488-1495.
270. Kumar MSA, Xiao SG, Fyfe B, et al. Steroid avoidance in renal transplantation using basiliximab induction, cyclosporine-based immunosuppression and protocol biopsies. *Clin Transplant.* 2005;19(1):61-69.
271. Barros VR, Rocha V, Garcia VD, Garcia CD. Anaphylactic shock after retreatment with basiliximab. *Transplant Proc.* 2003;35(1):579.
272. Baudouin V, Crusiaux A, Haddad E, et al. Anaphylactic shock caused by immunoglobulin E sensitization after retreatment with the chimeric anti-interleukin-2 receptor monoclonal antibody basiliximab. *Transplantation.* 2003;76(3):459-463.
273. Leonard PA, Woodside KJ, Gugliuzza KK, Sur S, Daller JA. Safe administration of a humanized murine antibody after anaphylaxis to a chimeric murine antibody. *Transplantation.* 2002;74(12):1697-1700.
274. *Simulect for Injection Prescribing Information.* East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2005.
275. Sifontis NM, Benedetti E, Vasquez EM. Clinically significant drug interaction between basiliximab and tacrolimus in renal transplant recipients. *Transplant Proc.* 2002;34(5):1730-1732.
276. Kovarik JM, Offner G, Broyer M, et al. A rational dosing algorithm for basiliximab (Simulect) in pediatric renal transplantation based on pharmacokinetic-dynamic evaluations. *Transplantation.* 2002;74(7):966-971.
277. Moreno A, Maestre J, Balcells J, et al. Lung transplantation in young infants with interstitial pneumonia. *Transplant Proc.* 2003;35(5):1951-1953.
278. SIMULECT, basiliximab [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2000.
279. Vincenti F, Kirkman R, Light S, et al; Daclizumab Triple Therapy Study Group. Interleukin-2-receptor blockade with daclizumab to prevent acute rejection in renal transplantation. *N Engl J Med.* 1998;338(3):161-165.
280. Nashan B, Light S, Hardie IR, Lin A, Johnson JR; Daclizumab Double Therapy Study Group. Reduction of acute renal allograft rejection by daclizumab. *Transplantation.* 1999; 67(1):110-115.
281. Beniaminovitz A, Itescu S, Lietz K, et al. Prevention of rejection in cardiac transplantation by blockade of the interleukin-2 receptor with a monoclonal antibody. *N Engl J Med.* 2000;342(9):613-619.

282. Nair MP, Nampoory MR, Johnny KV, et al. Induction immunosuppression with interleukin-2 receptor antibodies (basiliximab and daclizumab) in renal transplant recipients. *Transplant Proc.* 2001;33(5):2767-2769.
283. Ciancio G, Burke GW, Suzart K, et al. Effect of daclizumab, tacrolimus and mycophenolate mofetil in racial minority first renal transplant recipients. *Transplant Proc.* 2002;34(5):1617-1618.
284. Pescovitz MD, Bumgardner G, Gaston RS, et al. Pharmacokinetics of daclizumab and mycophenolate mofetil with cyclosporine and steroids in renal transplantation. *Clin Transplant.* 2003;17(6):511-517.
285. Lee SJ, Zahrieh D, Agura E, et al. Effect of up-front daclizumab when combined with steroids for the treatment of acute graft-versus-host disease: results of a randomized trial. *Blood.* 2004;104(5):1559-1564.
286. Boillot O, Mayer DA, Boudjema K, et al. Corticosteroid-free immunosuppression with tacrolimus following induction with daclizumab: a large randomized clinical study. *Liver Transpl.* 2005;11(1):61-67.
287. Hershberger RE, Starling RC, Eisen HJ, et al. Daclizumab to prevent rejection after cardiac transplantation. *N Engl J Med.* 2005;352(26):2705-2713.
288. Rostaing L, Cantarovich D, Mourad G, et al; CARMEN Study Group. Corticosteroid-free immunosuppression with tacrolimus, mycophenolate mofetil, and daclizumab induction in renal transplantation. *Transplantation.* 2005;79(7):807-814.
289. Stratta RJ, Alloway RR, Lo A, Hodge EE. A prospective, randomized, multicenter study evaluating the safety and efficacy of two dosing regimens of daclizumab compared to no antibody induction in simultaneous kidney-pancreas transplantation: results at 3 years. *Transplant Proc.* 2005;37(8):3531-3534.
290. Stratta RJ, Alloway RR, Lo A, Hodge EE. Risk factors and outcomes analyses at 36 months of a prospective, randomized, multicenter, trial of daclizumab induction in simultaneous kidney-pancreas transplant recipients. *Transplant Proc.* 2005;37(8):3527-3530.
291. Dresske B, Haendlschke F, Lenz P, et al. WOFIE stimulates regulatory T cells: a 2-year follow-up of renal transplant recipients. *Transplantation.* 2006;81(11):1549-1557.
292. Van Assche G, Sandborn WJ, Feagan BG, et al. Daclizumab, a humanised monoclonal antibody to the interleukin 2 receptor (CD25), for the treatment of moderately to severely active ulcerative colitis: a randomised, double blind, placebo controlled, dose ranging trial. *Gut.* 2006;55(11):1568-1574.
293. Garrity ER Jr, Villanueva J, Bhorade SM, Husain AN, Vigneswaran WT. Low rate of acute lung allograft rejection after the use of daclizumab, an interleukin 2 receptor antibody. *Transplantation.* 2001;71(6):773-777.
294. Bhorade SM, Lurain NS, Jordan A, et al. Emergence of ganciclovir-resistant cytomegalovirus in lung transplant recipients. *J Heart Lung Transplant.* 2002;21(12):1274-1282.
295. Bhorade SM, Jordan A, Villanueva J, et al. Comparison of three tacrolimus-based immunosuppressive regimens in lung transplantation. *Am J Transplant.* 2003;3(12):1570-1575.
296. Weill D, Lock BJ, Wewers DL, et al. Combination prophylaxis with ganciclovir and cytomegalovirus (CMV) immune globulin after lung transplantation: effective CMV prevention following daclizumab induction. *Am J Transplant.* 2003;3(4):492-496.
297. Burton CM, Andersen CB, Jensen AS, et al. The incidence of acute cellular rejection after lung transplantation: a comparative study of anti-thymocyte globulin and daclizumab. *J Heart Lung Transplant.* 2006;25(6):638-647.
298. Gordon R. 2003 Safety Alert: Zenapax (Daclizumab). Rockville, MD: Food and Drug Administration; 2003.
299. Vincenti F, Lantz M, Birnbaum J, et al. A phase I trial of humanized anti-interleukin 2 receptor antibody in renal transplantation. *Transplantation.* 1997;63(1):33-38.
300. *Daclizumab Prescribing Information.* Nutley, NJ: Hoffmann-La Roche Inc; 2005.
301. Chin C, Pittson S, Luikart H, et al. Induction therapy for pediatric and adult heart transplantation: comparison between OKT3 and daclizumab. *Transplantation.* 2005;80(4):477-481.
302. Stratta RJ, Alloway RR, Lo A, Hodge EE. Two-dose daclizumab regimen in simultaneous kidney-pancreas transplant recipients: primary endpoint analysis of a multicenter, randomized study. *Transplantation.* 2003;75(8):1260-1266.
303. Stratta RJ, Alloway RR, Lo A, Hodge EE; PIVOT Study Group. One-year outcomes in simultaneous kidney-pancreas transplant recipients receiving an alternative dosing regimen of daclizumab. *Transplant Proc.* 2004;36(4):1080-1081.
304. Heffron TG, Pillen T, Smallwood GA, Welch D, Oakley B, Romero R. Pediatric liver transplantation with daclizumab induction. *Transplantation.* 2003;75(12):2040-2043.
305. Sarwal MM, Vidhun JR, Alexander SR, Satterwhite T, Millan M, Salvatierra O Jr. Continued superior outcomes with modification and lengthened follow-up of a steroid-avoidance pilot with extended daclizumab induction in pediatric renal transplantation. *Transplantation.* 2003;76(9):1331-1339.
306. ZENAPAX IV injection, daclizumab IV injection [package insert]. Nutley, NJ: Roche Pharmaceuticals; 2005.
307. Chapman TM, Keating GM. Basiliximab: a review of its use as induction therapy in renal transplantation. *Drugs.* 2003;63(24):2803-2835.
308. Jayne D, Rasmussen N, Andrassy K, et al; European Vasculitis Study Group. A randomized trial of maintenance therapy for vasculitis associated with antineutrophil cytoplasmic autoantibodies. *N Engl J Med.* 2003;349(1):36-44.
309. Brown JW, Turrentine MW, Kesler KA, et al. Triple-drug immunosuppression for heart transplantation in infants and children. *J Heart Lung Transplant.* 1993;12(6 pt 2):S265-S274.
310. Eisen HJ, Kobashigawa J, Keogh A, et al; Mycophenolate Mofetil Cardiac Study Investigators. Three-year results of a randomized, double-blind, controlled trial of mycophenolate mofetil versus azathioprine in cardiac transplant recipients. *J Heart Lung Transplant.* 2005;24(5):517-525.
311. McNeil K, Glanville AR, Wahlers T, et al. Comparison of mycophenolate mofetil and azathioprine for prevention of bronchiolitis obliterans syndrome in de novo lung transplant recipients. *Transplantation.* 2006;81(7):998-1003.
312. Palmer SM, Baz MA, Sanders L, et al. Results of a randomized, prospective, multicenter trial of mycophenolate mofetil versus azathioprine in the prevention of acute lung allograft rejection. *Transplantation.* 2001;71(12):1772-1776.
313. Pirenne J, Aerts R, Koshiha T, et al. Steroid-free immunosuppression during and after liver transplantation—a 3-yr follow-up report. *Clin Transplant.* 2003;17(3):177-182.
314. Remuzzi G, Cravedi P, Costantini M, et al. Mycophenolate mofetil versus azathioprine for prevention of chronic allograft dysfunction in renal transplantation: the MYSS follow-up randomized, controlled clinical trial. *J Am Soc Nephrol.* 2007;18(6):1973-1985.
315. Rigotti P, Cadrobbi R, Baldan N, et al. Mycophenolate mofetil (MMF) versus azathioprine (AZA) in pancreas transplantation: a single-center experience. *Clin Nephrol.* 2000;53(suppl 4):52-54.
316. Snell GI, Valentine VG, Vitulo P, et al; RAD B159 Study Group. Everolimus versus azathioprine in maintenance lung transplant recipients: an international, randomized,

- double-blind clinical trial. *Am J Transplant*. 2006;6(1):169-177.
317. Wiesner R, Rabkin J, Klintmalm G, et al. A randomized double-blind comparative study of mycophenolate mofetil and azathioprine in combination with cyclosporine and corticosteroids in primary liver transplant recipients. *Liver Transpl*. 2001;7(5):442-450.
318. Cohen JM, Miller A, Spiera H. Interstitial pneumonitis complicating rheumatoid arthritis. Sustained remission with azathioprine therapy. *Chest*. 1977;72(4):521-524.
319. Greenwood AJ, Stanford MR, Graham EM. The role of azathioprine in the management of retinal vasculitis. *Eye (Lond)*. 1998;12(pt 5):783-788.
320. Müller-Quernheim J, Kienast K, Held M, Pfeifer S, Costabel U. Treatment of chronic sarcoidosis with an azathioprine/prednisolone regimen. *Eur Respir J*. 1999;14(5):1117-1122.
321. Laszlo A, Espolio Y, Auckenthaler A, Michel JP, Janssens JP. Azathioprine and low-dose corticosteroids for the treatment of cryptogenic organizing pneumonia in an older patient. *J Am Geriatr Soc*. 2003;51(3):433-434.
322. Raghu G, Depaso WJ, Cain K, et al. Azathioprine combined with prednisone in the treatment of idiopathic pulmonary fibrosis: a prospective double-blind, randomized, placebo-controlled clinical trial. *Am Rev Respir Dis*. 1991;144(2):291-296.
323. Dheda K, Laloo UG, Cassim B, Mody GM. Experience with azathioprine in systemic sclerosis associated with interstitial lung disease. *Clin Rheumatol*. 2004;23(4):306-309.
324. Hoyles RK, Ellis RW, Wellsbury J, et al. A multicenter, prospective, randomized, double-blind, placebo-controlled trial of corticosteroids and intravenous cyclophosphamide followed by oral azathioprine for the treatment of pulmonary fibrosis in scleroderma. *Arthritis Rheum*. 2006;54(12):3962-3970.
325. McCarty MJ, Lillis P, Vukelja SJ. Azathioprine as a steroid-sparing agent in radiation pneumonitis. *Chest*. 1996;109(5):1397-1400.
326. Demedts M, Behr J, Buhl R, et al; IFIGENIA Study Group. High-dose acetylcysteine in idiopathic pulmonary fibrosis. *N Engl J Med*. 2005;353(21):2229-2242.
327. Connell WR, Kamm MA, Ritchie JK, Lennard-Jones JE. Bone marrow toxicity caused by azathioprine in inflammatory bowel disease: 27 years of experience. *Gut*. 1993;34(8):1081-1085.
328. Sturdevant RA, Singleton JW, Deren JL, Law DH, McCleery JL. Azathioprine-related pancreatitis in patients with Crohn's disease. *Gastroenterology*. 1979;77(4 pt 2):883-886.
329. Dubinsky MC, Vasiliauskas EA, Singh H, et al. 6-thioguanine can cause serious liver injury in inflammatory bowel disease patients. *Gastroenterology*. 2003;125(2):298-303.
330. Jeurissen ME, Boerbooms AM, van de Putte LB. Pancytopenia related to azathioprine in rheumatoid arthritis. *Ann Rheum Dis*. 1988;47(6):503-505.
331. Kibukamusoke JW. Malaria prophylaxis and immunosuppressant therapy in management of nephrotic syndrome associated with quartan malaria. *Arch Dis Child*. 1968;43(231):598-600.
332. Hagaman JT, Kinder BW, Eckman MH. Thiopurine S-methyltransferase testing in idiopathic pulmonary fibrosis: a pharmacogenetic cost-effectiveness analysis. *Lung*. 2010;188(2):125-132.
333. Cuffari C, Théorêt Y, Latour S, Seidman G. 6-Mercaptopurine metabolism in Crohn's disease: correlation with efficacy and toxicity. *Gut*. 1996;39(3):401-406.
334. Dubinsky MC, Lamothe S, Yang HY, et al. Pharmacogenomics and metabolite measurement for 6-mercaptopurine therapy in inflammatory bowel disease. *Gastroenterology*. 2000;118(4):705-713.
335. Kirschner BS. Safety of azathioprine and 6-mercaptopurine in pediatric patients with inflammatory bowel disease. *Gastroenterology*. 1998;115(4):813-821.
336. Wilson BE, Parsonnet J. Azathioprine hypersensitivity mimicking sepsis in a patient with Crohn's disease. *Clin Infect Dis*. 1993;17(5):940-941.
337. Rundles RW, Wyngaarden JB, Hitchings GH. Effects of xanthine oxidase inhibitor on thiopurine metabolism, hyperuricemia, and gout. *Trans Assoc Am Physicians*. 1963;76:126-140.
338. Gossman J, Kachel HG, Schoeppe W, Scheuermann EH. Anemia in renal transplant recipients caused by concomitant therapy with azathioprine and angiotensin-converting enzyme inhibitors. *Transplantation*. 1993;56(3):585-589.
339. Centers for Disease Control (CDC). General recommendations on immunization. *MMWR Morb Mortal Wkly Rep*. 1989;38(13):205-214, 219-227.
340. Havrda DE, Rathbun S, Scheid D. A case report of warfarin resistance due to azathioprine and review of the literature. *Pharmacotherapy*. 2001;21(3):355-357.
341. Chaparro M, Trapero-Marugán M, Moreno-Otero R, Gisbert JP. Azathioprine plus ribavirin treatment and pancytopenia. *Aliment Pharmacol Ther*. 2009;30(9):962-963.
342. Peyrin-Biroulet L, Cadranet JF, Noursbaum JB, et al. Interaction of ribavirin with azathioprine metabolism potentially induces myelosuppression. *Aliment Pharmacol Ther*. 2008;28(8):984-993.
343. Alstead EM, Ritchie JK, Lennard-Jones JE, Farthing MJ, Clark ML. Safety of azathioprine in pregnancy in inflammatory bowel disease. *Gastroenterology*. 1990;99(2):443-446.
344. Källén B. The teratogenicity of antirheumatic drugs—what is the evidence? *Scand J Rheumatol Suppl*. 1998;107:119-124.
345. Armenti VT, Radomski JS, Moritz MJ, et al; National Transplantation Pregnancy Registry. Report from the National Transplantation Pregnancy Registry (NTPR): outcomes of pregnancy after transplantation. *Clin Transpl*. 2002;121-130.
346. Pirson Y, Van Lierde M, Ghysen J, Squifflet JP, Alexandre GP, van Ypersele de Strihou C. Retardation of fetal growth in patients receiving immunosuppressive therapy. *N Engl J Med*. 1985;313(5):328.
347. Scott JR. Fetal growth retardation associated with maternal administration of immunosuppressive drugs. *Am J Obstet Gynecol*. 1977;128(6):668-676.
348. Saarikoski S, Seppälä M. Immunosuppression during pregnancy: transmission of azathioprine and its metabolites from the mother to the fetus. *Am J Obstet Gynecol*. 1973;115(8):1100-1106.
349. Coté CJ, Meuwissen HJ, Pickering RJ. Effects on the neonate of prednisone and azathioprine administered to the mother during pregnancy. *J Pediatr*. 1974;85(3):324-328.
350. Gaffney K, Scott DG. Azathioprine and cyclophosphamide in the treatment of rheumatoid arthritis. *Br J Rheumatol*. 1998;37(8):824-836.
351. Aronoff GR, Bennett WM, Berns JS, et al. *Drug Prescribing in Renal Failure: Dosing Guidelines for Adults and Children*. 5th ed. Philadelphia, PA: American College of Physicians; 2007.
352. De Groot K, Rasmussen N, Bacon PA, et al. Randomized trial of cyclophosphamide versus methotrexate for induction of remission in early systemic antineutrophil cytoplasmic antibody-associated vasculitis. *Arthritis Rheum*. 2005;52(8):2461-2469.
353. Doty JD, Mazur JE, Judson MA. Treatment of corticosteroid-resistant neurosarcoidosis with a short-course cyclophosphamide regimen. *Chest*. 2003;124(5):2023-2026.

354. Lower EE, Broderick JP, Brott TG, Baughman RP. Diagnosis and management of neurological sarcoidosis. *Arch Intern Med.* 1997;157(16):1864-1868.
355. Johnson MA, Kwan S, Snell NJ, Nunn AJ, Darbyshire JH, Turner-Warwick M. Randomised controlled trial comparing prednisolone alone with cyclophosphamide and low dose prednisolone in combination in cryptogenic fibrosing alveolitis. *Thorax.* 1989;44(4):280-288.
356. Zisman DA, Lynch JP III, Toews GB, Kazerooni EA, Flint A, Martinez FJ. Cyclophosphamide in the treatment of idiopathic pulmonary fibrosis: a prospective study in patients who failed to respond to corticosteroids. *Chest.* 2000;117(6):1619-1626.
357. Tashkin DP, Elashoff R, Clements PJ, et al; Scleroderma Lung Study Research Group. Cyclophosphamide versus placebo in scleroderma lung disease. *N Engl J Med.* 2006;354(25):2655-2666.
358. Smyth CJ, Bartholomew BA, Mills DM, Steigerwald JC, Strong SJ, Recart S. Cyclophosphamide therapy for rheumatoid arthritis. *Arch Intern Med.* 1975;135(6):789-793.
359. Baughman RP, Lower EE. Use of intermittent, intravenous cyclophosphamide for idiopathic pulmonary fibrosis. *Chest.* 1992;102(4):1090-1094.
360. Girling DJ, Stott H, Stephens RJ, Fox W. Fifteen-year follow-up of all patients in a study of post-operative chemotherapy for bronchial carcinoma. *Br J Cancer.* 1985;52(6):867-873.
361. Talar-Williams C, Hijazi YM, Walther MM, et al. Cyclophosphamide-induced cystitis and bladder cancer in patients with Wegener granulomatosis. *Ann Intern Med.* 1996;124(5):477-484.
362. Knight A, Askling J, Granath F, Sparen P, Ekblom A. Urinary bladder cancer in Wegener's granulomatosis: risks and relation to cyclophosphamide. *Ann Rheum Dis.* 2004;63(10):1307-1311.
363. Stott H, Stephens R, Fox W, Simon G, Roy DC. An investigation of the chest radiographs in a controlled trial of busulphan, cyclophosphamide, and a placebo after resection for carcinoma of the lung. *Thorax.* 1976;31(3):265-270.
364. Gonzalez-Lopez L, Cardona-Muñoz EG, Celis A, et al. Therapy with intermittent pulse cyclophosphamide for pulmonary hypertension associated with systemic lupus erythematosus. *Lupus.* 2004;13(2):105-112.
365. Radis CD, Kahl LE, Baker GL, et al. Effects of cyclophosphamide on the development of malignancy and on long-term survival of patients with rheumatoid arthritis. A 20-year followup study. *Arthritis Rheum.* 1995;38(8):1120-1127.
366. Hesselstrand R, Scheja A, Akesson A. Mortality and causes of death in a Swedish series of systemic sclerosis patients. *Ann Rheum Dis.* 1998;57(11):682-686.
367. Gould VE, Miller J. Sclerosing alveolitis induced by cyclophosphamide. Ultrastructural observations on alveolar injury and repair. *Am J Pathol.* 1975;81(3):513-530.
368. Siemann DW, Macler L, Penney DP. Cyclophosphamide-induced pulmonary toxicity. *Br J Cancer Suppl.* 1986;7:343-346.
369. Malik SW, Myers JL, DeRemee RA, Specks U. Lung toxicity associated with cyclophosphamide use. Two distinct patterns. *Am J Respir Crit Care Med.* 1996;154(6 pt 1):1851-1856.
370. Kirshon B, Wasserstrum N, Willis R, Herman GE, McCabe ER. Teratogenic effects of first-trimester cyclophosphamide therapy. *Obstet Gynecol.* 1988;72(3 pt 2):462-464.
371. Somers EC, Marder W, Christman GM, Ognenovski V, McCune WJ. Use of a gonadotropin-releasing hormone analog for protection against premature ovarian failure during cyclophosphamide therapy in women with severe lupus. *Arthritis Rheum.* 2005;52(9):2761-2767.
372. Ramsey-Goldman R, Mientus JM, Kutzer JE, Mulvihill JJ, Medsger TA Jr. Pregnancy outcome in women with systemic lupus erythematosus treated with immunosuppressive drugs. *J Rheumatol.* 1993;20(7):1152-1157.
373. Lower EE, Blau R, Gazder P, Tummala R. The risk of premature menopause induced by chemotherapy for early breast cancer. *J Womens Health Gend Based Med.* 1999;8(7):949-954.
374. Emery P, Breedveld FC, Lemmel EM, et al. A comparison of the efficacy and safety of leflunomide and methotrexate for the treatment of rheumatoid arthritis. *Rheumatology (Oxford).* 2000;39(6):655-665.
375. Smolen JS, Kalden JR, Scott DL, et al; European Leflunomide Study Group. Efficacy and safety of leflunomide compared with placebo and sulphasalazine in active rheumatoid arthritis: a double-blind, randomised, multicentre trial. *Lancet.* 1999;353(9149):259-266.
376. Strand V, Cohen S, Schiff M, et al; Leflunomide Rheumatoid Arthritis Investigators Group. Treatment of active rheumatoid arthritis with leflunomide compared with placebo and methotrexate. *Arch Intern Med.* 1999;159(21):2542-2550.
377. Cohen S, Cannon GW, Schiff M, et al; Utilization of Leflunomide in the Treatment of Rheumatoid Arthritis Trial Investigator Group. Two-year, blinded, randomized, controlled trial of treatment of active rheumatoid arthritis with leflunomide compared with methotrexate. *Arthritis Rheum.* 2001;44(9):1984-1992.
378. Kalden JR, Schattenkirchner M, Sörensen H, et al. The efficacy and safety of leflunomide in patients with active rheumatoid arthritis: a five-year followup study. *Arthritis Rheum.* 2003;48(6):1513-1520.
379. van Woerkom JM, Kruize AA, Geenen R, et al. Safety and efficacy of leflunomide in primary Sjögren's syndrome: a phase II pilot study. *Ann Rheum Dis.* 2007;66(8):1026-1032.
380. Tam LS, Li EK, Wong CK, Lam CW, Szeto CC. Double-blind, randomized, placebo-controlled pilot study of leflunomide in systemic lupus erythematosus. *Lupus.* 2004;13(8):601-604.
381. Metzler C, Fink C, Lamprecht P, Gross WL, Reinhold-Keller E. Maintenance of remission with leflunomide in Wegener's granulomatosis. *Rheumatology (Oxford).* 2004;43(3):315-320.
382. Baughman RP, Lower EE. Leflunomide for chronic sarcoidosis. *Sarcoidosis Vasc Diffuse Lung Dis.* 2004;21(1):43-48.
383. Lange U, Piegsa M, Müller-Ladner U, Strunk J. Anti-Jo-1 antibody positive polymyositis—successful therapy with leflunomide. *Autoimmunity.* 2006;39(3):261-264.
384. Handler RP. Leflunomide for relapsing polychondritis: successful longterm treatment. *J Rheumatol.* 2006;33(9):1916.
385. Pirildar T. Treatment of adult-onset Still's disease with leflunomide and chloroquine combination in two patients. *Clin Rheumatol.* 2003;22(2):157.
386. Sebastiani M, Giuggioli D, Vesprini E, Caruso A, Ferri C. Successful treatment with leflunomide of arthritis in systemic sclerosis patients. *Rheumatology (Oxford).* 2006;45(9):1175-1176.
387. Hardinger KL, Wang CD, Schnitzler MA, et al. Prospective, pilot, open-label, short-term study of conversion to leflunomide reverses chronic renal allograft dysfunction. *Am J Transplant.* 2002;2(9):867-871.
388. Waldman WJ, Knight DA, Lurain NS, et al. Novel mechanism of inhibition of cytomegalovirus by the experimental

- immunosuppressive agent leflunomide. *Transplantation*. 1999;68(6):814-825.
389. Avery RK, Bolwell BJ, Yen-Lieberman B, et al. Use of leflunomide in an allogeneic bone marrow transplant recipient with refractory cytomegalovirus infection. *Bone Marrow Transplant*. 2004;34(12):1071-1075.
 390. John GT, Manivannan J, Chandy S, et al. A prospective evaluation of leflunomide therapy for cytomegalovirus disease in renal transplant recipients. *Transplant Proc*. 2005; 37(10):4303-4305.
 391. Scott DL, Smolen JS, Kalden JR, et al; European Leflunomide Study Group. Treatment of active rheumatoid arthritis with leflunomide: two year follow up of a double blind, placebo controlled trial versus sulfasalazine. *Ann Rheum Dis*. 2001;60(10):913-923.
 392. Kaltwasser JP, Nash P, Gladman D, et al; Treatment of Psoriatic Arthritis Study Group. Efficacy and safety of leflunomide in the treatment of psoriatic arthritis and psoriasis: a multinational, double-blind, randomized, placebo-controlled clinical trial. *Arthritis Rheum*. 2004;50(6):1939-1950.
 393. Poór G, Strand V; Leflunomide Multinational Study Group. Efficacy and safety of leflunomide 10 mg versus 20 mg once daily in patients with active rheumatoid arthritis: multinational double-blind, randomized trial. *Rheumatology (Oxford)*. 2004;43(6):744-749.
 394. Silverman E, Mouy R, Spiegel L, et al; Leflunomide in Juvenile Rheumatoid Arthritis (JRA) Investigator Group. Leflunomide or methotrexate for juvenile rheumatoid arthritis. *N Engl J Med*. 2005;352(16):1655-1666.
 395. Karanikolas G, Charalambopoulos D, Andrianakos A, Antoniadou C, Katsilambros N. Combination of cyclosporine and leflunomide versus single therapy in severe rheumatoid arthritis. *J Rheumatol*. 2006;33(3):486-489.
 396. Rozman B. Clinical pharmacokinetics of leflunomide. *Clin Pharmacokinet*. 2002;41(6):421-430.
 397. *Labeling Information: Leflunomide*. Rockville, MD: Food and Drug Administration; 2005.
 398. Olsen NJ, Stein CM. New drugs for rheumatoid arthritis. *N Engl J Med*. 2004;350(21):2167-2179.
 399. Matteson E, Cush JJ. *Hotline: Reports of Leflunomide Hepatotoxicity in Patients With Rheumatoid Arthritis*. Atlanta, GA: American College of Rheumatology; 2001.
 400. Bharadwaj A, Haroon N. Peripheral neuropathy in patients on leflunomide. *Rheumatology (Oxford)*. 2004;43(7):934.
 401. Bonnel RA, Graham DJ. Peripheral neuropathy in patients treated with leflunomide. *Clin Pharmacol Ther*. 2004;75(6): 580-585.
 402. Carulli MT, Davies UM. Peripheral neuropathy: an unwanted effect of leflunomide? *Rheumatology (Oxford)*. 2002;41(8): 952-953.
 403. Richards BL, Spies J, McGill N, et al. Effect of leflunomide on the peripheral nerves in rheumatoid arthritis. *Intern Med J*. 2007;37(2):101-107.
 404. Fischer TW, Bauer HI, Graefe T, Barta U, Elsner P. Erythema multiforme-like drug eruption with oral involvement after intake of leflunomide. *Dermatology*. 2003; 207(4):386-389.
 405. Shastri V, Betkerur J, Kushalappa PA, Savita TG, Parthasarathi G. Severe cutaneous adverse drug reaction to leflunomide: a report of five cases. *Indian J Dermatol Venereol Leprol*. 2006;72(4):286-289.
 406. Savage RL, Highton J, Boyd IW, Chapman P. Pneumonitis associated with leflunomide: a profile of New Zealand and Australian reports. *Intern Med J*. 2006;36(3):162-169.
 407. Takeishi M, Akiyama Y, Akiba H, Adachi D, Hirano M, Mimura T. Leflunomide induced acute interstitial pneumonia. *J Rheumatol*. 2005;32(6):1160-1163.
 408. Sakai F, Noma S, Kurihara Y, et al. Leflunomide-related lung injury in patients with rheumatoid arthritis: imaging features. *Mod Rheumatol*. 2005;15(3):173-179.
 409. Suissa S, Hudson M, Ernst P. Leflunomide use and the risk of interstitial lung disease in rheumatoid arthritis. *Arthritis Rheum*. 2006;54(5):1435-1439.
 410. Perez-Ruiz F, Nolla JM. Influence of leflunomide on renal handling of urate and phosphate in patients with rheumatoid arthritis. *J Clin Rheumatol*. 2003;9(4):215-218.
 411. Ramsey-Goldman R, Schilling E. Immunosuppressive drug use during pregnancy. *Rheum Dis Clin North Am*. 1997; 23(1):149-167.
 412. Baughman RP, Winget DB, Lower EE. Methotrexate is steroid sparing in acute sarcoidosis: results of a double blind, randomized trial. *Sarcoidosis Vasc Diffuse Lung Dis*. 2000;17(1):60-66.
 413. Lower EE, Baughman RP. The use of low dose methotrexate in refractory sarcoidosis. *Am J Med Sci*. 1990;299(3):153-157.
 414. Lower EE, Baughman RP. Prolonged use of methotrexate for sarcoidosis. *Arch Intern Med*. 1995;155(8):846-851.
 415. Webster GF, Razsi LK, Sanchez M, Shupack JL. Weekly low-dose methotrexate therapy for cutaneous sarcoidosis. *J Am Acad Dermatol*. 1991;24(3):451-454.
 416. Dev S, McCallum RM, Jaffe GJ. Methotrexate treatment for sarcoid-associated panuveitis. *Ophthalmology*. 1999;106(1):111-118.
 417. Kaye O, Palazzo E, Grossin M, Bourgeois P, Kahn MF, Malaise MG. Low-dose methotrexate: an effective corticosteroid-sparing agent in the musculoskeletal manifestations of sarcoidosis. *Br J Rheumatol*. 1995;34(7):642-644.
 418. Agbogu BN, Stern BJ, Sewell C, Yang G. Therapeutic considerations in patients with refractory neurosarcoidosis. *Arch Neurol*. 1995;52(9):875-879.
 419. Mullarkey MF, Blumenstein BA, Andrade WP, Bailey GA, Olason I, Wetzel CE. Methotrexate in the treatment of corticosteroid-dependent asthma. A double-blind crossover study. *N Engl J Med*. 1988;318(10):603-607.
 420. Comet R, Domingo C, Larrosa M, et al. Benefits of low weekly doses of methotrexate in steroid-dependent asthmatic patients. A double-blind, randomized, placebo-controlled study. *Respir Med*. 2006;100(3):411-419.
 421. de Groot K, Mühler M, Reinhold-Keller E, Paulsen J, Gross WL. Induction of remission in Wegener's granulomatosis with low dose methotrexate. *J Rheumatol*. 1998;25(3):492-495.
 422. de Groot K, Reinhold-Keller E, Tatsis E, et al. Therapy for the maintenance of remission in sixty-five patients with generalized Wegener's granulomatosis. Methotrexate versus trimethoprim/sulfamethoxazole. *Arthritis Rheum*. 1996; 39(12):2052-2061.
 423. Egerer G, Witzens M, Spaeth A, et al. Successful treatment of bronchiolitis obliterans organizing pneumonia with low-dose methotrexate in a patient with Hodgkin's disease. *Oncology*. 2001;61(1):23-27.
 424. Douglas WW, Tazelaar HD, Hartman TE, et al. Polymyositis-dermatomyositis-associated interstitial lung disease. *Am J Respir Crit Care Med*. 2001;164(7):1182-1185.
 425. Metzler C, Hellmich B, Gause A, Gross WL, de Groot K. Churg Strauss syndrome—successful induction of remission with methotrexate and unexpected high cardiac and pulmonary relapse ratio during maintenance treatment. *Clin Exp Rheumatol*. 2004;22(6)(suppl 36):S52-S61.
 426. Cahill BC, O'Rourke MK, Strasburg KA, et al. Methotrexate for lung transplant recipients with steroid-resistant acute rejection. *J Heart Lung Transplant*. 1996;15(11):1130-1137.
 427. Shiner RJ, Nunn AJ, Chung KF, Geddes DM. Randomised, double-blind, placebo-controlled trial of methotrexate in steroid-dependent asthma. *Lancet*. 1990;336(8708):137-140.

428. Dyer PD, Vaughan TR, Weber RW. Methotrexate in the treatment of steroid-dependent asthma. *J Allergy Clin Immunol*. 1991;88(2):208-212.
429. Erzurum SC, Leff JA, Cochran JE, et al. Lack of benefit of methotrexate in severe, steroid-dependent asthma. A double-blind, placebo-controlled study. *Ann Intern Med*. 1991;114(5):353-360.
430. Taylor DR, Flannery EM, Herbison GP. Methotrexate in the management of severe steroid dependent asthma. *N Z Med J*. 1993;106(964):409-411.
431. Coffey MJ, Sanders G, Eschenbacher WL, et al. The role of methotrexate in the management of steroid-dependent asthma. *Chest*. 1994;105(1):117-121.
432. Stewart GE II, Diaz JD, Lockey RF, Seleznick MJ, Trudeau WL, Ledford DK. Comparison of oral pulse methotrexate with placebo in the treatment of severe glucocorticosteroid-dependent asthma. *J Allergy Clin Immunol*. 1994;94(3 pt 1):482-489.
433. Kanzow G, Nowak D, Magnussen H. Short term effect of methotrexate in severe steroid-dependent asthma. *Lung*. 1995;173(4):223-231.
434. Ogirala RG, Sturm TM, Aldrich TK, et al. Single, high-dose intramuscular triamcinolone acetonide versus weekly oral methotrexate in life-threatening asthma: a double-blind study. *Am J Respir Crit Care Med*. 1995;152(5 pt 1):1461-1466.
435. Hedman J, Seideman P, Albertioni F, Stenius-Aarniala B. Controlled trial of methotrexate in patients with severe chronic asthma. *Eur J Clin Pharmacol*. 1996;49(5):347-349.
436. Metzler C, Miehle N, Manger K, et al; German Network of Rheumatic Diseases. Elevated relapse rate under oral methotrexate versus leflunomide for maintenance of remission in Wegener's granulomatosis. *Rheumatology (Oxford)*. 2007;46(7):1087-1091.
437. Mullarkey MF, Lammert JK, Blumenstein BA. Long-term methotrexate treatment in corticosteroid-dependent asthma. *Ann Intern Med*. 1990;112(8):577-581.
438. Shiner RJ, Katz I, Shulimzon T, Silkoff P, Benzaray S. Methotrexate in steroid-dependent asthma: long-term results. *Allergy*. 1994;49(7):565-568.
439. Sneller MC, Hoffman GS, Talar-Williams C, Kerr GS, Hallahan CW, Fauci AS. An analysis of forty-two Wegener's granulomatosis patients treated with methotrexate and prednisone. *Arthritis Rheum*. 1995;38(5):608-613.
440. Yew WW, Lee J, Wong PC, Wong CF, Chau CH. Low-dose methotrexate in the management of Chinese patients with steroid-dependent asthma. *Drugs Exp Clin Res*. 1996;22(6):317-321.
441. Gedalia A, Molina JF, Ellis GS Jr, Galen W, Moore C, Espinoza LR. Low-dose methotrexate therapy for childhood sarcoidosis. *J Pediatr*. 1997;130(1):25-29.
442. Langford CA, Talar-Williams C, Barron KS, Sneller MC. A staged approach to the treatment of Wegener's granulomatosis: induction of remission with glucocorticoids and daily cyclophosphamide switching to methotrexate for remission maintenance. *Arthritis Rheum*. 1999;42(12):2666-2673.
443. Reinhold-Keller E, Fink CO, Herlyn K, Gross WL, De Groot K. High rate of renal relapse in 71 patients with Wegener's granulomatosis under maintenance of remission with low-dose methotrexate. *Arthritis Rheum*. 2002;47(3):326-332.
444. Vucinic VM. What is the future of methotrexate in sarcoidosis? A study and review. *Curr Opin Pulm Med*. 2002;8(5):470-476.
445. Langford CA, Talar-Williams C, Barron KS, Sneller MC. Use of a cyclophosphamide-induction methotrexate-maintenance regimen for the treatment of Wegener's granulomatosis: extended follow-up and rate of relapse. *Am J Med*. 2003;114(6):463-469.
446. Furst DE, Erikson N, Clute L, Koehnke R, Burmeister LF, Kohler JA. Adverse experience with methotrexate during 176 weeks of a longterm prospective trial in patients with rheumatoid arthritis. *J Rheumatol*. 1990;17(12):1628-1635.
447. Weinblatt ME, Coblyn JS, Fox DA, et al. Efficacy of low-dose methotrexate in rheumatoid arthritis. *N Engl J Med*. 1985;312(13):818-822.
448. Wijnands MJ, van Riel PL, Gribnau FW, van de Putte LB. Risk factors of second-line antirheumatic drugs in rheumatoid arthritis. *Semin Arthritis Rheum*. 1990;19(6):337-352.
449. McKendry RJ, Dale P. Adverse effects of low dose methotrexate therapy in rheumatoid arthritis. *J Rheumatol*. 1993;20(11):1850-1856.
450. McKendry RJ, Cyr M. Toxicity of methotrexate compared with azathioprine in the treatment of rheumatoid arthritis. A case-control study of 131 patients. *Arch Intern Med*. 1989;149(3):685-689.
451. Kinder AJ, Hassell AB, Brand J, Brownfield A, Grove M, Shadforth MF. The treatment of inflammatory arthritis with methotrexate in clinical practice: treatment duration and incidence of adverse drug reactions. *Rheumatology (Oxford)*. 2005;44(1):61-66.
452. Weinblatt ME, Weissman BN, Holdsworth DE, et al. Long-term prospective study of methotrexate in the treatment of rheumatoid arthritis. 84-month update. *Arthritis Rheum*. 1992;35(2):129-137.
453. Weinblatt ME, Maier AL, Fraser PA, Coblyn JS. Longterm prospective study of methotrexate in rheumatoid arthritis: conclusion after 132 months of therapy. *J Rheumatol*. 1998;25(2):238-242.
454. Hargreaves MR, Mowat AG, Benson MK. Acute pneumonitis associated with low dose methotrexate treatment for rheumatoid arthritis: report of five cases and review of published reports. *Thorax*. 1992;47(8):628-633.
455. Salaffi F, Manganelli P, Carotti M, Subiaco S, Lamanna G, Cervini C. Methotrexate-induced pneumonitis in patients with rheumatoid arthritis and psoriatic arthritis: report of five cases and review of the literature. *Clin Rheumatol*. 1997;16(3):296-304.
456. Zisman DA, McCune WJ, Tino G, Lynch JP III. Drug-induced pneumonitis: the role of methotrexate. *Sarcoidosis Vasc Diffuse Lung Dis*. 2001;18(3):243-252.
457. Dawson JK, Graham DR, Desmond J, Fewins HE, Lynch MP. Investigation of the chronic pulmonary effects of low-dose oral methotrexate in patients with rheumatoid arthritis: a prospective study incorporating HRCT scanning and pulmonary function tests. *Rheumatology (Oxford)*. 2002;41(3):262-267.
458. Roenigk HH Jr, Auerbach R, Maibach HI, Weinstein GD. Methotrexate guidelines—revised. *J Am Acad Dermatol*. 1982;6(2):145-155.
459. Whiting-O'Keefe QE, Fye KH, Sack KD. Methotrexate and histologic hepatic abnormalities: a meta-analysis. *Am J Med*. 1991;90(6):711-716.
460. Walker AM, Funch D, Dreyer NA, et al. Determinants of serious liver disease among patients receiving low-dose methotrexate for rheumatoid arthritis. *Arthritis Rheum*. 1993;36(3):329-335.
461. Baughman RP, Koehler A, Bejarano PA, Lower EE, Weber FL Jr. Role of liver function tests in detecting methotrexate-induced liver damage in sarcoidosis. *Arch Intern Med*. 2003;163(5):615-620.
462. Kremer JM, Alarcón GS, Lightfoot RW Jr, et al; American College of Rheumatology. Methotrexate for rheumatoid

- arthritis. Suggested guidelines for monitoring liver toxicity. *Arthritis Rheum.* 1994;37(3):316-328.
463. Aithal GP, Haugk B, Das S, Card T, Burt AD, Record CO. Monitoring methotrexate-induced hepatic fibrosis in patients with psoriasis: are serial liver biopsies justified? *Aliment Pharmacol Ther.* 2004;19(4):391-399.
464. Erickson AR, Reddy V, Vogelgesang SA, West SG. Usefulness of the American College of Rheumatology recommendations for liver biopsy in methotrexate-treated rheumatoid arthritis patients. *Arthritis Rheum.* 1995;38(8):1115-1119.
465. Fathi NH, Mitros F, Hoffman J, et al. Longitudinal measurement of methotrexate liver concentrations does not correlate with liver damage, clinical efficacy, or toxicity during a 3.5 year double blind study in rheumatoid arthritis. *J Rheumatol.* 2002;29(10):2092-2098.
466. Taylor WJ, Korendowych E, Nash P, et al. Drug use and toxicity in psoriatic disease: focus on methotrexate. *J Rheumatol.* 2008;35(7):1454-1457.
467. Beyeler C, Reichen J, Thomann SR, Lauterburg BH, Gerber NJ. Quantitative liver function in patients with rheumatoid arthritis treated with low-dose methotrexate: a longitudinal study. *Br J Rheumatol.* 1997;36(3):338-344.
468. Mok MY, Ng WL, Yuen MF, Wong RW, Lau CS. Safety of disease modifying anti-rheumatic agents in rheumatoid arthritis patients with chronic viral hepatitis. *Clin Exp Rheumatol.* 2000;18(3):363-368.
469. Evans WE, Pratt CB. Effect of pleural effusion on high-dose methotrexate kinetics. *Clin Pharmacol Ther.* 1978;23(1):68-72.
470. Li J, Gwilt P. The effect of malignant effusions on methotrexate disposition. *Cancer Chemother Pharmacol.* 2002;50(5):373-382.
471. Morgan SL, Baggott JE, Vaughn WH, et al. Supplementation with folic acid during methotrexate therapy for rheumatoid arthritis. A double-blind, placebo-controlled trial. *Ann Intern Med.* 1994;121(11):833-841.
472. van Ede AE, Laan RF, Rood MJ, et al. Effect of folic or folinic acid supplementation on the toxicity and efficacy of methotrexate in rheumatoid arthritis: a forty-eight week, multicenter, randomized, double-blind, placebo-controlled study. *Arthritis Rheum.* 2001;44(7):1515-1524.
473. van Ede AE, Laan RF, Blom HJ, et al. Homocysteine and folate status in methotrexate-treated patients with rheumatoid arthritis. *Rheumatology (Oxford).* 2002;41(6):658-665.
474. Østensen M, Motta M. Therapy insight: the use of anti-rheumatic drugs during nursing. *Nat Clin Pract Rheumatol.* 2007;3(7):400-406.
475. Maetzel A, Wong A, Strand V, Tugwell P, Wells G, Bombardier C. Meta-analysis of treatment termination rates among rheumatoid arthritis patients receiving disease-modifying anti-rheumatic drugs. *Rheumatology (Oxford).* 2000;39(9):975-981.
476. Lewden B, Vial T, Elefant E, Nelva A, Carlier P, Descotes J; French Network of Regional Pharmacovigilance Centers. Low dose methotrexate in the first trimester of pregnancy: results of a French collaborative study. *J Rheumatol.* 2004;31(12):2360-2365.
477. Lloyd ME, Carr M, McElhatton P, Hall GM, Hughes RA. The effects of methotrexate on pregnancy, fertility and lactation. *QJM.* 1999;92(10):551-563.
478. Baughman RP, Lower EE. A clinical approach to the use of methotrexate for sarcoidosis. *Thorax.* 1999;54(8):742-746.
479. Pavy S, Constantin A, Pham T, et al. Methotrexate therapy for rheumatoid arthritis: clinical practice guidelines based on published evidence and expert opinion. *Joint Bone Spine.* 2006;73(4):388-395.
480. Ortiz-Alvarez O, Morishita K, Avery G, et al. Guidelines for blood test monitoring of methotrexate toxicity in juvenile idiopathic arthritis. *J Rheumatol.* 2004;31(12):2501-2506.
481. CellCept, mycophenolate mofetil [package insert]. Nutley, NJ: Roche Laboratories; 2003.
482. Gerbase MW, Fathi M, Spiliopoulos A, Rochat T, Nicod LP. Pharmacokinetics of mycophenolic acid associated with calcineurin inhibitors: long-term monitoring in stable lung recipients with and without cystic fibrosis. *J Heart Lung Transplant.* 2003;22(5):587-590.
483. O'Hair DP, Cantu E, McGregor C, et al. Preliminary experience with mycophenolate mofetil used after lung transplantation. *J Heart Lung Transplant.* 1998;17(9):864-868.
484. Soccacal PM, Gasche Y, Favre H, Spiliopoulos A, Nicod LP. Improvement of drug-induced chronic renal failure in lung transplantation. *Transplantation.* 1999;68(1):164-165.
485. Zuckermann A, Birsan T, Thaghavi S, et al. Benefit of mycophenolate mofetil in patients with cyclosporine A-induced nephropathy after lung transplantation. *Transplant Proc.* 1999;31(1-2):1160-1161.
486. Groetzner J, Wittwer T, Kaczmarek I, et al. Conversion to sirolimus and mycophenolate can attenuate the progression of bronchiolitis obliterans syndrome and improves renal function after lung transplantation. *Transplantation.* 2006;81(3):355-360.
487. Sen HN, Suhler EB, Al-Khatib SQ, Djalilian AR, Nussenblatt RB, Buggage RR. Mycophenolate mofetil for the treatment of scleritis. *Ophthalmology.* 2003;110(9):1750-1755.
488. Kilmartin DJ, Forrester JV, Dick AD. Rescue therapy with mycophenolate mofetil in refractory uveitis. *Lancet.* 1998;352(9121):35-36.
489. Contreras G, Pardo V, Leclercq B, et al. Sequential therapies for proliferative lupus nephritis. *N Engl J Med.* 2004;350(10):971-980.
490. Grotz W, von Zedtwitz I, Andre M, Schollmeyer P. Treatment of retroperitoneal fibrosis by mycophenolate mofetil and corticosteroids. *Lancet.* 1998;352(9135):1195.
491. Goldblum R. Therapy of rheumatoid arthritis with mycophenolate mofetil. *Clin Exp Rheumatol.* 1993;11(suppl 8):S117-S119.
492. Langford CA, Talar-Williams C, Sneller MC. Mycophenolate mofetil for remission maintenance in the treatment of Wegener's granulomatosis. *Arthritis Rheum.* 2004;51(2):278-283.
493. Kouba DJ, Mimouni D, Rencic A, Nousari HC. Mycophenolate mofetil may serve as a steroid-sparing agent for sarcoidosis. *Br J Dermatol.* 2003;148(1):147-148.
494. Samad AS, Lindsley CB. Treatment of pulmonary hemorrhage in childhood systemic lupus erythematosus with mycophenolate mofetil. *South Med J.* 2003;96(7):705-707.
495. Swigris JJ, Olson AL, Fischer A, et al. Mycophenolate mofetil is safe, well tolerated, and preserves lung function in patients with connective tissue disease-related interstitial lung disease. *Chest.* 2006;130(1):30-36.
496. European Mycophenolate Mofetil Cooperative Study Group. Placebo-controlled study of mycophenolate mofetil combined with cyclosporin and corticosteroids for prevention of acute rejection. *Lancet.* 1995;345(8961):1321-1325.
497. Sollinger HW; US Renal Transplant Mycophenolate Mofetil Study Group. Mycophenolate mofetil for the prevention of acute rejection in primary cadaveric renal allograft recipients. *Transplantation.* 1995;60(3):225-232.
498. Kobashigawa JA, Renlund DG, Gerosa G, et al; ERL2401 Heart Study Investigators. Similar efficacy and safety of

- enteric-coated mycophenolate sodium (EC-MPS, myfortic) compared with mycophenolate mofetil (MMF) in de novo heart transplant recipients: results of a 12-month, single-blind, randomized, parallel-group, multicenter study. *J Heart Lung Transplant*. 2006;25(8):935-941.
499. Taketomo CKHJ, Kraus DM. *Pediatric Dosage Handbook*. 4th ed. Hudson, OH: Lexi-Comp Inc.; 1997.
 500. Manito N, Kaplinsky EJ, Bernat R, et al. Fatal interstitial pneumonitis associated with sirolimus therapy in a heart transplant recipient. *J Heart Lung Transplant*. 2004;23(6):780-782.
 501. CellCept, mycophenolate mofetil [package insert]. Nutley, NJ: Roche Laboratories Inc.; 2000.
 502. Deierhoi MH, Kauffman RS, Hudson SL, et al. Experience with mycophenolate mofetil (RS61443) in renal transplantation at a single center. *Ann Surg*. 1993;217(5):476-482.
 503. Ensley RD, Bristow MR, Olsen SL, et al. The use of mycophenolate mofetil (RS-61443) in human heart transplant recipients. *Transplantation*. 1993;56(1):75-82.
 504. Engelen W, Verpooten GA, Van der Planken M, Helbert MF, Bosmans JL, De Broe ME. Four cases of red blood cell aplasia in association with the use of mycophenolate mofetil in renal transplant patients. *Clin Nephrol*. 2003;60(2):119-124.
 505. Moreso F, Serón D, Morales JM, et al. Incidence of leukopenia and cytomegalovirus disease in kidney transplants treated with mycophenolate mofetil combined with low cyclosporine and steroid doses. *Clin Transplant*. 1998;12(3):198-205.
 506. Epinette WW, Parker CM, Jones EL, Greist MC. Mycophenolic acid for psoriasis. A review of pharmacology, long-term efficacy, and safety. *J Am Acad Dermatol*. 1987;17(6):962-971.
 507. Gallagher H, Andrews PA. Cytomegalovirus infection and abdominal pain with mycophenolate mofetil: is there a link? *Drug Saf*. 2001;24(6):405-412.
 508. Sollinger HW, Belzer FO, Deierhoi MH, et al. RS-61443 (mycophenolate mofetil). A multicenter study for refractory kidney transplant rejection. *Ann Surg*. 1992;216(4):513-518.
 509. CellCept, mycophenolate mofetil [package insert]. Nutley, NJ: Roche Laboratories; 1998.
 510. Morii M, Ueno K, Ogawa A, et al. Impairment of mycophenolate mofetil absorption by iron ion. *Clin Pharmacol Ther*. 2000;68(6):613-616.
 511. Meiser BM, Pfeiffer M, Schmidt D, et al. Combination therapy with tacrolimus and mycophenolate mofetil following cardiac transplantation: importance of mycophenolic acid therapeutic drug monitoring. *J Heart Lung Transplant*. 1999;18(2):143-149.
 512. van Gelder T, Le Meur Y, Shaw LM, et al. Therapeutic drug monitoring of mycophenolate mofetil in transplantation. *Ther Drug Monit*. 2006;28(2):145-154.
 513. Kahan BD, Kaplan B, Lorber MI, Winkler M, Cambon N, Boger RS. RAD in de novo renal transplantation: comparison of three doses on the incidence and severity of acute rejection. *Transplantation*. 2001;71(10):1400-1406.
 514. Dunn C, Croom KF. Everolimus: a review of its use in renal and cardiac transplantation. *Drugs*. 2006;66(4):547-570.
 515. Patel JK, Kobashigawa JA. Everolimus: an immunosuppressive agent in transplantation. *Expert Opin Pharmacother*. 2006;7(10):1347-1355.
 516. Doyle RL, Hertz MI, Dunitz JM, et al. RAD in stable lung and heart/lung transplant recipients: safety, tolerability, pharmacokinetics, and impact of cystic fibrosis. *J Heart Lung Transplant*. 2001;20(3):330-339.
 517. Rapamune, sirolimus [package insert]. Philadelphia, PA: Wyeth Pharmaceuticals; 2007.
 518. Sehgal SN. Rapamune (sirolimus, rapamycin): an overview and mechanism of action. *Ther Drug Monit*. 1995;17(6):660-665.
 519. Moses JW, Leon MB, Popma JJ, et al; SIRIUS Investigators. Sirolimus-eluting stents versus standard stents in patients with stenosis in a native coronary artery. *N Engl J Med*. 2003;349(14):1315-1323.
 520. Hartford CM, Ratain MJ. Rapamycin: something old, something new, sometimes borrowed and now renewed. *Clin Pharmacol Ther*. 2007;82(4):381-388.
 521. Taveira-DaSilva AM, Hathaway O, Stylianou M, Moss J. Changes in lung function and chylous effusions in patients with lymphangioleiomyomatosis treated with sirolimus. *Ann Intern Med*. 2011;154(12):797-805.
 522. McCormack FX, Inoue Y, Moss J, et al; National Institutes of Health Rare Lung Diseases Consortium; MILES Trial Group. Efficacy and safety of sirolimus in lymphangioleiomyomatosis. *N Engl J Med*. 2011;364(17):1595-1606.
 523. Bissler JJ, McCormack FX, Young LR, et al. Sirolimus for angiomylipoma in tuberous sclerosis complex or lymphangioleiomyomatosis. *N Engl J Med*. 2008;358(2):140-151.
 524. Bhorade S, Baz M, Ahya V, et al. Comparison of a tacrolimus/sirolimus/prednisone regimen versus tacrolimus/azathioprine/prednisone immunosuppressive regimen in lung transplantation. *J Heart Lung Transplant*. 2008;27(2):S207.
 525. Kahan BD; The Rapamune US Study Group. Efficacy of sirolimus compared with azathioprine for reduction of acute renal allograft rejection: a randomised multicentre study. *Lancet*. 2000;356(9225):194-202.
 526. MacDonald AS; RAPAMUNE Global Study Group. A worldwide, phase III, randomized, controlled, safety and efficacy study of a sirolimus/cyclosporine regimen for prevention of acute rejection in recipients of primary mismatched renal allografts. *Transplantation*. 2001;71(2):271-280.
 527. Murgia MG, Jordan S, Kahan BD. The side effect profile of sirolimus: a phase I study in quiescent cyclosporine-prednisone-treated renal transplant patients. *Kidney Int*. 1996;49(1):209-216.
 528. Kandaswamy R, Melancon JK, Dunn T, et al. A prospective randomized trial of steroid-free maintenance regimens in kidney transplant recipients—an interim analysis. *Am J Transplant*. 2005;5(6):1529-1536.
 529. Mendez R, Gonwa T, Yang HC, Weinstein S, Jensik S, Steinberg S; Prograf Study Group. A prospective, randomized trial of tacrolimus in combination with sirolimus or mycophenolate mofetil in kidney transplantation: results at 1 year. *Transplantation*. 2005;80(3):303-309.
 530. Amigues L, Klouche K, Massanet P, et al. Sirolimus-associated acute respiratory distress syndrome in a renal transplant recipient. *Transplant Proc*. 2005;37(6):2830-2831.
 531. Bankar RN, Kumar S, Köhnke A. Sirolimus-induced interstitial pneumonitis. *J Postgrad Med*. 2006;52(4):329.
 532. Bauer C, Lidove O, Lamotte C, et al. Sirolimus-associated interstitial pneumonitis in a renal transplant patient [in French]. *Rev Med Interne*. 2006;27(3):248-252.
 533. Champion L, Stern M, Israël-Biet D, et al. Brief communication: sirolimus-associated pneumonitis: 24 cases in renal transplant recipients. *Ann Intern Med*. 2006;144(7):505-509.
 534. Adibelli Z, Dilek M, Kocak B, Tülek N, Uzun O, Akpolat T. An unusual presentation of sirolimus associated cough in a renal transplant recipient. *Transplant Proc*. 2007;39(10):3463-3464.
 535. Morath C, Schwenger V, Ksoll-Rudek D, et al. Four cases of sirolimus-associated interstitial pneumonitis: identification of risk factors. *Transplant Proc*. 2007;39(1):99-102.

536. Lennon A, Finan K, FitzGerald MX, McCormick PA. Interstitial pneumonitis associated with sirolimus (rapamycin) therapy after liver transplantation. *Transplantation*. 2001;72(6):1166-1167.
537. Howard L, Gopalan D, Griffiths M, Mahadeva R. Sirolimus-induced pulmonary hypersensitivity associated with a CD4 T-cell infiltrate. *Chest*. 2006;129(6):1718-1721.
538. Jiménez Pérez M, Olmedo Martín R, Marín García D, Lozano Rey JM, de la Cruz Lombardo J, Rodrigo López JM. Pulmonary toxicity associated with sirolimus therapy in liver transplantation [in Spanish]. *Gastroenterol Hepatol*. 2006;29(10):616-618.
539. Pérez MJ, Martín RO, García DM, Rey JM, de la Cruz Lombardo J, Rodrigo López JM. Interstitial pneumonitis associated with sirolimus in liver transplantation: a case report. *Transplant Proc*. 2007;39(10):3498-3499.
540. Roberts RJ, Wells AC, Unitt E, et al. Sirolimus-induced pneumonitis following liver transplantation. *Liver Transpl*. 2007;13(6):853-856.
541. Lindenfeld JA, Simon SF, Zamora MR, et al. BOOP is common in cardiac transplant recipients switched from a calcineurin inhibitor to sirolimus. *Am J Transplant*. 2005;5(6):1392-1396.
542. Delgado JF, Torres J, José Ruiz-Cano M, et al. Sirolimus-associated interstitial pneumonitis in 3 heart transplant recipients. *J Heart Lung Transplant*. 2006;25(9):1171-1174.
543. Das BB, Shoemaker L, Subramanian S, Johnsrude C, Recto M, Austin EH. Acute sirolimus pulmonary toxicity in an infant heart transplant recipient: case report and literature review. *J Heart Lung Transplant*. 2007;26(3):296-298.
544. David S, Kümpers P, Shin H, Haller H, Fliser D. Everolimus-associated interstitial pneumonitis in a patient with a heart transplant. *Nephrol Dial Transplant*. 2007;22(11):3363-3364.
545. King-Biggs MB, Dunitz JM, Park SJ, Kay Savik S, Hertz MI. Airway anastomotic dehiscence associated with use of sirolimus immediately after lung transplantation. *Transplantation*. 2003;75(9):1437-1443.
546. Groetzner J, Kur F, Spelsberg F, et al; Munich Lung Transplant Group. Airway anastomosis complications in de novo lung transplantation with sirolimus-based immunosuppression. *J Heart Lung Transplant*. 2004;23(5):632-638.
547. Guilbeau JM. Delayed wound healing with sirolimus after liver transplant. *Ann Pharmacother*. 2002;36(9):1391-1395.
548. Dean PG, Lund WJ, Larson TS, et al. Wound-healing complications after kidney transplantation: a prospective, randomized comparison of sirolimus and tacrolimus. *Transplantation*. 2004;77(10):1555-1561.
549. Albengres E, Le Louet H, Tillement JP. Immunosuppressive drugs and pregnancy: experimental and clinical data. *Transplant Proc*. 1997;29(5):2461-2466.
550. EBPG Expert Group on Renal Transplantation. European best practice guidelines for renal transplantation. Section IV: long-term management of the transplant recipient. IV.10. Pregnancy in renal transplant recipients. *Nephrol Dial Transplant*. 2002;17(suppl 4):50-55.
551. MacDonald A, Scarola J, Burke JT, Zimmerman JJ. Clinical pharmacokinetics and therapeutic drug monitoring of sirolimus. *Clin Ther*. 2000;22(suppl B):B101-B121.
552. Fox R. Anti-malarial drugs: possible mechanisms of action in autoimmune disease and prospects for drug development. *Lupus*. 1996;5(suppl 1):S4-S10.
553. Yam JC, Kwok AK. Ocular toxicity of hydroxychloroquine. *Hong Kong Med J*. 2006;12(4):294-304.
554. Hirsch JG. Experimental treatment with chloroquine. *Am Rev Respir Dis*. 1961;84(5):52-58.
555. Morse SI, Cohn ZA, Hirsch JG, Schaefer RW. The treatment of sarcoidosis with chloroquine. *Am J Med*. 1961;30:779-784.
556. Davies D. Sarcoidosis treated with chloroquine. *Br J Dis Chest*. 1963;57:30-36.
557. Siltzbach LE, Teirstein AS. Chloroquine therapy in 43 patients with intrathoracic and cutaneous sarcoidosis. *Acta Med Scand Suppl*. 1964;425:302-308.
558. Davies D, Curwen MP. Chloroquine in the treatment of sarcoidosis. A report from the Research Committee of the British Tuberculosis Association. *Tubercle*. 1967;48(4):257-272.
559. Krasnitz A. Chloroquine therapy in pulmonary sarcoidosis. *N Y State J Med*. 1967;67(12):1729-1736.
560. Brodthagen H. Chloroquine in pulmonary sarcoidosis. *Lancet*. 1968;291(7552):1157.
561. Johns CJ. Sarcoidosis. *Med Sect Proc*. 1986;:19-28.
562. O'Leary TJ, Jones G, Yip A, Lohnes D, Cohan M, Yendt ER. The effects of chloroquine on serum 1,25-dihydroxyvitamin D and calcium metabolism in sarcoidosis. *N Engl J Med*. 1986;315(12):727-730.
563. Baltzan M, Mehta S, Kirkham TH, Cosio MG. Randomized trial of prolonged chloroquine therapy in advanced pulmonary sarcoidosis. *Am J Respir Crit Care Med*. 1999;160(1):192-197.
564. Osika E, Muller MH, Boccon-Gibod L, et al. Idiopathic pulmonary fibrosis in infants. *Pediatr Pulmonol*. 1997;23(1):49-54.
565. Jones E, Callen JP. Hydroxychloroquine is effective therapy for control of cutaneous sarcoid granulomas. *J Am Acad Dermatol*. 1990;23(3 pt 1):487-489.
566. Costedoat-Chalumeau N, Hulot JS, Amoura Z, et al. Cardiomyopathy related to antimalarial therapy with illustrative case report. *Cardiology*. 2007;107(2):73-80.
567. Nord JE, Shah PK, Rinaldi RZ, Weisman MH. Hydroxychloroquine cardiotoxicity in systemic lupus erythematosus: a report of 2 cases and review of the literature. *Semin Arthritis Rheum*. 2004;33(5):336-351.
568. Stein M, Bell MJ, Ang LC. Hydroxychloroquine neuromyotoxicity. *J Rheumatol*. 2000;27(12):2927-2931.
569. Baguet JP, Tremel F, Fabre M. Chloroquine cardiomyopathy with conduction disorders. *Heart*. 1999;81(2):221-223.
570. Costedoat-Chalumeau N, Hulot JS, Amoura Z, et al. Heart conduction disorders related to antimalarials toxicity: an analysis of electrocardiograms in 85 patients treated with hydroxychloroquine for connective tissue diseases. *Rheumatology (Oxford)*. 2007;46(5):808-810.
571. Edwards AC, Meredith TJ, Sowton E. Complete heart block due to chronic chloroquine toxicity managed with permanent pacemaker. *BMJ*. 1978;1(6120):1109-1110.
572. Newton-Cheh C, Lin AE, Baggish AL, Wang H. Case records of the Massachusetts General Hospital. Case 11-2011. A 47-year-old man with systemic lupus erythematosus and heart failure. *N Engl J Med*. 2011;364(15):1450-1460.
573. Brachman PS Jr, Metchock B, Kozarsky PE. Effects of antimalarial chemoprophylactic agents on the viability of the Ty21a typhoid vaccine strain. *Clin Infect Dis*. 1992;15(6):1057-1058.
574. Horowitz H, Carbonaro CA. Inhibition of the *Salmonella typhi* oral vaccine strain, Ty21a, by mefloquine and chloroquine. *J Infect Dis*. 1992;166(6):1462-1464.
575. Pappaioanou M, Fishbein DB, Dreesen DW, et al. Antibody response to preexposure human diploid-cell rabies vaccine given concurrently with chloroquine. *N Engl J Med*. 1986;314(5):280-284.
576. Rennie IG. Clinically important ocular reactions to systemic drug therapy. *Drug Saf*. 1993;9(3):196-211.
577. Elder M, Rahman AM, McLay J. Early paracentral visual field loss in patients taking hydroxychloroquine. *Arch Ophthalmol*. 2006;124(12):1729-1733.

578. Estes ML, Ewing-Wilson D, Chou SM, et al. Chloroquine neuromyotoxicity. Clinical and pathologic perspective. *Am J Med.* 1987;82(3):447-455.
579. Ziering CL, Rabinowitz LG, Esterly NB. Antimalarials for children: indications, toxicities, and guidelines. *J Am Acad Dermatol.* 1993;28(5 pt 1):764-770.
580. Jones SK. Ocular toxicity and hydroxychloroquine: guidelines for screening. *Br J Dermatol.* 1999;140(1):3-7.
581. Silman A, Shipley M. Ophthalmological monitoring for hydroxychloroquine toxicity: a scientific review of available data. *Br J Rheumatol.* 1997;36(5):599-601.
582. Costedoat-Chalumeau N, Amoura Z, Duhaut P, et al. Safety of hydroxychloroquine in pregnant patients with connective tissue diseases: a study of one hundred thirty-three cases compared with a control group. *Arthritis Rheum.* 2003;48(11):3207-3211.
583. Mazzuca SA, Yung R, Brandt KD, Yee RD, Katz BP. Current practices for monitoring ocular toxicity related to hydroxychloroquine (Plaquenil) therapy. *J Rheumatol.* 1994;21(1):59-63.
584. Moen MD, McKeage K, Plosker GL, Siddiqui MA. Imatinib: a review of its use in chronic myeloid leukaemia. *Drugs.* 2007;67(2):299-320.
585. Daniels CE, Wilkes MC, Edens M, et al. Imatinib mesylate inhibits the profibrogenic activity of TGF-beta and prevents bleomycin-mediated lung fibrosis. *J Clin Invest.* 2004;114(9):1308-1316.
586. Ghofrani HA, Seeger W, Grimminger F. Imatinib for the treatment of pulmonary arterial hypertension. *N Engl J Med.* 2005;353(13):1412-1413.
587. Patterson KC, Weissmann A, Ahmadi T, Farber HW. Imatinib mesylate in the treatment of refractory idiopathic pulmonary arterial hypertension. *Ann Intern Med.* 2006;145(2):152-153.
588. O'Brien SG, Guilhot F, Larson RA, et al; IRIS Investigators. Imatinib compared with interferon and low-dose cytarabine for newly diagnosed chronic-phase chronic myeloid leukemia. *N Engl J Med.* 2003;348(11):994-1004.
589. Verweij J, Casali PG, Zalcberg J, et al. Progression-free survival in gastrointestinal stromal tumours with high-dose imatinib: randomised trial. *Lancet.* 2004;364(9440):1127-1134.
590. Zöhlhöfer D, Hausleiter J, Kastrati A, et al. A randomized, double-blind, placebo-controlled trial on restenosis prevention by the receptor tyrosine kinase inhibitor imatinib. *J Am Coll Cardiol.* 2005;46(11):1999-2003.
591. Van Glabbeke M, Verweij J, Casali PG, et al. Predicting toxicities for patients with advanced gastrointestinal stromal tumours treated with imatinib: a study of the European Organisation for Research and Treatment of Cancer, the Italian Sarcoma Group, and the Australasian Gastro-Intestinal Trials Group (EORTC-ISG-AGITG). *Eur J Cancer.* 2006;42(14):2277-2285.
592. GLEEVEC oral tablets, imatinib mesylate oral tablets [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2007.
593. Imatinib mesylate [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2006.
594. Yamasawa H, Sugiyama Y, Bando M, Ohno S. Drug-induced pneumonitis associated with imatinib mesylate in a patient with idiopathic pulmonary fibrosis. *Respiration.* 2008;75(3):350-354.
595. Yokoyama T, Miyazawa K, Kurakawa E, et al. Interstitial pneumonia induced by imatinib mesylate: pathologic study demonstrates alveolar destruction and fibrosis with eosinophilic infiltration. *Leukemia.* 2004;18(3):645-646.
596. Russell MA, Carpenter MW, Akhtar MS, Lagattuta TF, Egorin MJ. Imatinib mesylate and metabolite concentrations in maternal blood, umbilical cord blood, placenta and breast milk. *J Perinatol.* 2007;27(4):241-243.