Practice guidelines for pharmacists: The pharmacological management of rheumatoid arthritis with traditional and biologic disease-modifying antirheumatic drugs

Carolyn Bornstein, BScPhm, ACPR, CGP, FCSHP, RPh; Marie Craig, BScPhm, RPh;
Diane Tin, BScPhm, CDE, CGP, RPh

Background and treatment options for rheumatoid arthritis

Rheumatoid arthritis (RA) is a chronic autoimmune disease characterized by inflammation, pain, stiffness and progressive joint destruction. It currently affects about 1% of Canadians and can occur at any age but is most often recognized between the ages of 25 and 50 years, occurring in women 3 times more frequently than in men.¹ More recently, elderly-onset RA (EORA), occurring after age 60 years, has been described. This form of RA has a prevalence of about 2% and represents 10% to 33% of all RA cases. In EORA, the female bias is less marked than in younger age groups. In this population, RA can be misdiagnosed as osteoarthritis (OA).²

Pharmacists should be able to identify people with possible signs of RA, as the disease can be very destructive, especially if inadequately treated. At a glance, the hands of a patient with RA may present with soft, swollen, large and middle knuckle finger joints on one or both hands, whereas OA will present as large, hard, bony middle and end knuckles on the fingers (on one or both hands).

Patients with RA not only have a higher rate of morbidity and mortality but also experience significant financial and productivity losses as well as symptom-related emotional and social burdens affecting their quality of life. The pharmacological management of RA has progressed substantially over the last decade. Earlier and more aggressive treatment strategies with traditional disease-modifying antirheumatic drugs (DMARDs) and the more recent introduction of biologic therapies that target specific mechanisms of inflammation have been shown to alter the clinical course of RA and slow or halt radiographic progression.¹ However, early detection and treatment are necessary.

Based on a Canada-wide survey of rheumatologists and rheumatology health care providers, the Canadian Rheumatology Association (CRA) has developed recommendations for the pharmacological management of RA with traditional and biologic DMARDs in 2 parts: Part I provides focused treatment guidance,¹ and Part II provides focused guidance on safety aspects of the pharmacological management of RA.³ Presented here is an update on the pharmacological

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treatment of RA with input from the guidelines as applicable to pharmacists.

Diagnosis, treatment goals and monitoring

The goal of RA treatment is remission and, when not possible, minimal disease activity while controlling symptoms, halting damage, preventing disability and improving quality of life. Although inflammation is reversible, damage to the joints (erosion) is irreversible, hence the need for early aggressive treatment.

The presence of the following poor prognostic features should be assessed at baseline and considered when making treatment decisions: rheumatoid factor (RF) positivity, anti-cyclic citrullinated peptide (anti-CCP) antibody positivity, functional limitation, high number of swollen and tender joints, early erosions, extra-articular features, high erythrocyte sedimentation rate (ESR) and elevated C-reactive protein (CRP). It is important for pharmacists to be aware that while positive serology (RF and/or anti-CCP) results may indicate a patient with more aggressive (or active) disease, the diagnosis of RA is also based on clinical and physical examinations. Patients may have RA even if blood tests (ESR, CRP, RF and anti-CCP) are within the normal range. The anti-CCP antibody is a relatively new test that has a similar sensitivity but higher specificity for RA than RF and is a stronger predictor of erosive disease.⁴

Practice Tip: Encourage patients to undergo an anti-CCP blood test as ordered by their rheumatologist. This test may not be covered by government plans but may be covered by some health insurance plans.

Monitoring and treatment adjustments

Health care providers of RA should monitor disease activity as frequently as every 1 to 3 months in patients with active RA. Patients with well-controlled disease and those in remission can be monitored at longer intervals. Frequent assessments and follow-up for adjustments in treatment in unstable patients are associated with improved outcomes.

Practice Tip: Pharmacists are well positioned to remind patients with RA about the importance of keeping follow-up appointments and required monitoring such as laboratory tests or eye examinations. Adjustments in

therapy may include dosage changes, adding or switching DMARD therapies and possible short-term corticosteroid treatment either orally, by injection intramuscularly or directly into the joint(s).

Radiographs of the hands and feet are recommended as frequently as every 6 to 12 months in patients with recent-onset disease. Radiographs can be performed at longer intervals in patients with established disease. In RA, the goal is to prevent further joint damage being visible on radiographs. Also, DMARDs (which do not include nonsteroidal anti-inflammatory drugs [NSAIDs]) are required long term to control RA, even when symptoms no longer exist.

The first medication prescribed for arthritis pain is often an NSAID. It should be noted that NSAIDs are not included in the CRA guidelines as they are not DMARDs. Nevertheless, NSAIDs will be reviewed here briefly in light of their controversies and widespread use.

NSAIDs

Significantly, NSAIDs are used by more than 30 million people every day. Conaghan⁵ cites a 1997 survey that found that among prescription NSAID users, approximately 40% also use nonprescription NSAIDs at the same time, which reflects that even by 2012, we still know very little about how patients use these agents. Patients often unknowingly use multiple NSAIDs, yet the product insert and patient information rarely include a warning against this practice.

Practice Tip: Pharmacists should remind patients not to combine nonprescription NSAIDs with a prescription NSAID and not to take low-dose acetylsalicylic acid (ASA) unless it has been prescribed by a physician.

Rainsford and Bjarnason⁶ recently challenged the published and regulatory advice requiring that NSAIDs be taken with food or milk. The rationale is that foods confer a protective effect, but this has never actually been studied. Taking an NSAID in a fasting state is not a risk factor for causing gastrointestinal (GI) bleeding. This non-evidence-based advice may result in patients who skip breakfast also skipping their morning dose of medication, missing out on potential pain relief. Food can delay the onset of action without affecting bioavailability.⁶ This may be important when rapid onset of action is

preferable with the use of nonprescription NSAIDs on an as-needed basis.⁶

Risk factors for NSAID-associated GI injuries include high dose, increased age, *Helicobacter pylori* infection, history of gastric ulcers or ulcer complications and concomitant use of nonprescription NSAIDs, low-dose ASA, anticoagulants or corticosteroids.⁵ The use of proton pump inhibitors (PPIs) with NSAIDs may improve protection of the upper GI tract. Up to 0.5% of patients taking NSAIDs will have asymptomatic upper GI bleeding each year.⁷ It should be noted that symptoms of dyspepsia do not predict peptic ulceration, bleeding or perforation.⁸ Celecoxib is associated with a lower risk of ulcers and related complications than traditional NSAIDs (similar to that of a PPI plus NSAID), but these benefits are lost when it is combined with low-dose ASA.⁵ The NSAID with the greatest risk of GI toxicity is ketorolac.⁵

Practice Tip: Inform patients of the non-medication-related risks of a bleeding ulcer (e.g., *H. pylori*). These ulcers are usually painful. The use of an NSAID may hide ulcer pain, resulting in silent bleeding, so patients should be informed of the signs of GI bleeding (e.g., black, tarry, sticky stool). Signs of GI bleeding should be investigated for cause and treatment. However, GI symptoms while taking NSAIDs do not mean an ulcer is present.⁸

Enteric NSAID formulations are available, but they can also cause greater small intestinal damage.⁹ The cause of cardiovascular risks associated with NSAIDs is multifactorial. Initially felt to be an imbalance between COX-1 and COX-2, the risk is ascribed to the inhibition of prostaglandin production by vascular endothelial cells, including the cells that maintain plaque stability. A blood pressure (BP)-elevating effect of NSAIDs is also implicated in the cardiac risk profile.¹⁰ It has been reported that 100 mg of diclofenac daily increases the risk of a cardiovascular event.¹⁰ Although all NSAIDs increase cardiovascular risk, the risk appears to be least with naproxen.¹⁰

Practice Tip: In hypertensive patients, BP should be checked prior to NSAID initiation and after 1 to 4 weeks of therapy. Home BP monitoring is also recommended in elderly patients with chronic NSAID use.^{8,11} Pharmacists should discuss the benefits of symptom relief and cardiac risks with their patients. Recommending BP monitoring may help to alleviate the patient's

concerns. Because pain can increase BP, a pain-relieving NSAID may also lower BP.

Glucocorticoids

Glucocorticoids (oral, intramuscular or intra-articular) can be added to DMARD therapy as part of the initial treatment strategy of patients with RA and may be an option for managing flares, as bridge therapy while waiting for the DMARD to take effect or for symptom control if no other options exist. Glucocorticoids should be used in the lowest possible dose and tapered as rapidly as clinically feasible.¹

Glucocorticoids can be used when introducing a DMARD with a slow onset of action or in the short term during an RA flare.¹² Oral prednisone or intramuscular depot products can be used¹³ and are considered a low-risk treatment. An intra-articular glucocorticoid can be highly effective for active joints.¹² Intra-articular steroid products vary in solubility. Methylprednisolone is expected to last 7 days in the joint, while Habib and Miari¹⁴ report that triamcinolone hexacetonide could be retained in the knee joint for 2 to 3 weeks. Because of the rapid anti-inflammatory effect, the benefit from intra-articular injections usually lasts longer. A postinjection flare, described as increased pain and inflammation within hours of the injection, can occur following an intra-articular injection. This may be due to an acute inflammatory response to the cortisone ester crystals, and the symptoms can be controlled with ice and acetaminophen or NSAIDs and typically resolve within 48 hours. Prolonged or severe postinjection symptoms could be signs of an infection.¹⁵ Both oral and intramuscular cortisone can complicate glucose tolerance. Habib and Miari¹⁴ report that cortisone injected into the knee of patients with OA and diabetes resulted in increased blood sugar levels that returned to normal in 2.5 to 4 days.¹⁴

DMARDs (traditional)

Methotrexate (MTX) is the preferred DMARD with respect to efficacy and safety and should be the first one used in patients with RA unless contraindicated. No other traditional DMARD or anti-tumour necrosis factor (TNF) monotherapy has been shown to be superior to MTX in terms of clinical efficacy.¹ The safety profile of the weekly low doses used for RA treatment has been studied for over 25 years with very few clinically significant adverse effects.¹⁶ Ultimately, MTX

should be started orally or parenterally (doses may vary, but the CRA guidelines recommend 15 mg) and titrated to a usual maximum dose of 25 mg per week by rapid-dose escalation. The optimal schedule for dose escalation depends on the patient's clinical presentation and tolerance. Sometimes, the starting dose is 25 mg.^{1,17} In patients with an inadequate response or intolerance to oral MTX, parenteral administration should be considered.¹ When MTX is contraindicated, hydroxychloroquine, sulfasalazine and leflunomide are alternative DMARDs.¹

A recent review provided 10 reasons why the efficacy of MTX in RA is underestimated and related adverse events are overestimated.¹⁶ One reason was that the information in textbooks and websites commonly overemphasizes the adverse events and drug interactions associated with MTX while understating its "effects" on RA control.¹⁶

Does medication information available to community pharmacists contribute to this problem? General drug information for MTX is usually based on doses used for oncological purposes (ranging from 2000-3000 mg), for example, alopecia, severe nausea and vomiting. The NSAID-MTX interaction reported in many drug information databases is not clinically significant with the smaller weekly doses of MTX.¹⁷ A recent Cochrane review concluded that MTX can safely be used in combination with an NSAID, excluding anti-inflammatory doses of ASA, in the management of patients with inflammatory arthritis.¹⁸ High-dose ASA is no longer prescribed for use in RA.

Conversely, MTX and trimethoprim (2 antifolate agents) are an extremely serious and life-threatening combination that should be avoided. Increasing awareness by physicians, pharmacists and patients is essential to ensure safe and effective MTX therapy.^{17,19}

Practice Tip: A word of caution for pharmacists providing patient information on MTX: Make sure the information is based upon its use and dose for RA, not oncological use. A patient information handout about MTX for RA use and one on how to teach the patient to self-inject MTX subcutaneously are available on the CRA-approved website (www.rheuminfo.com) along with other patient-related rheumatology resources. The pharmacist should alert the prescriber and suggest possible alternatives to trimethoprim when it is prescribed for the patient

on MTX therapy. Unlike biologic DMARDs, MTX may be continued while the patient is on a course of antibiotics (excluding trimethoprim).¹⁷

What about the risk of infections with RA doses of MTX? It could be either the disease itself or the use of oral corticosteroids that is most often implicated in the literature.^{12,20} When 609 patients with RA were followed by the Mayo Clinic for a mean of 12.7 years, it was determined that patients with RA were at a greater risk for infections than patients without RA matched for age and comorbidities and that DMARD use, including MTX, did not contribute to this increased risk.²⁰

Can a patient taking MTX for RA drink alcohol? The lack of consensus and conflicting information (European vs North America)^{16,20-24} suggest that patients should discuss alcohol consumption with their rheumatologist. The impact of alcohol consumption may be reflected in the monthly liver function test results. Tilling et al.²⁵ define this as "transaminase levels (aspartate transaminase [AST] and alanine transaminase [ALT]) 3 times the upper limit of normal on 2 or more occasions when taken at trough level" (shortly before the MTX dose). Encourage patients to have their blood work done the day before their weekly MTX dose. If not discussed with the initiation of MTX, it is probably best for the patient to avoid alcohol until this has been clarified.

The 2011 CRA guidelines state that combination therapy with leflunomide and MTX should be used with caution, as this is associated with higher toxicity (GI, liver) and has no added benefit relative to other DMARD combinations.¹ However, several Canadian provincial formularies require patients to fail leflunomide or a combination of MTX and leflunomide before a biologic therapy can be used. Since the publication of the CRA guidelines, the 2013 SMILE study (Safety of MTX in Combination with Leflunomide in RA) comparing neutropenia and liver abnormalities in 2975 patients found that the combination of MTX and leflunomide was well tolerated, with adverse effects comparable to those of monotherapy and other nonbiologic DMARDs.²⁶ The study shows no increase in the rate of liver function test abnormalities with combined MTX and leflunomide therapy.²⁶

Practice Tip: Encourage regular blood-work monitoring for patients on MTX or leflunomide.

With MTX, encourage patients to have blood work done the day before their weekly dose.²⁵ Discourage the use of natural health products with known or suspected liver toxicity (e.g., valerian).²⁷

Initial combination therapy with traditional DMARDs should be considered, particularly in patients with poor prognostic factors, moderate to high disease activity and recent-onset disease.¹ Combination therapy should also be considered in patients who have an inadequate response to monotherapy. When treating with combination therapy, MTX should be used as the anchor drug unless contraindicated.¹ Combination therapy may include MTX and hydroxychloroquine, MTX and hydroxychloroquine and sulfasalazine, MTX and leflunomide or MTX and a biologic DMARD.

Biologic DMARDs (biologic response modifiers)

Many biologically derived DMARDs have been approved for the treatment of RA. They are categorized as TNF- α inhibitors or anti-TNFs (adalimumab, etanercept, infliximab, certolizumab and golimumab), B cell depleters (rituximab), T cell costimulation inhibitors (abatacept), interleukin-1 inhibitors (anakinra) and interleukin-6 inhibitors (tocilizumab). They are administered either by subcutaneous injection or intravenous infusion (Table 1).

Switching to a biologic after treatment failure of the MTX and leflunomide combination has been challenged in several recent trials utilizing triple DMARD therapy (hydroxychloroquine + MTX + sulfasalazine). O'Dell et al.²⁸ found that triple DMARD therapy was not inferior to etanercept and MTX. Isik et al.²⁹ found that one third of patients with MTX-resistant RA achieved remission on the cheaper, safer and easier-to-use triple DMARD therapy. DeJong³⁰ concluded that triple DMARD induction therapy is better than MTX monotherapy in early RA, and after 3 months, 50% fewer biologic DMARDs were prescribed in the combination therapy groups. Interestingly, all 3 studies used MTX orally. There is evidence to suggest better efficacy and less GI toxicity with subcutaneous MTX possibly due to the higher bioavailability.¹ Clinical experience with subcutaneous MTX in Canada is reported by the CATCH (Canadian Early Arthritis Cohort) observational study of best practice in treating early RA. Current data

from 8 Canadian sites and 1137 patients indicate that the strongest treatment predictors of good outcome were early use of subcutaneous MTX, triple DMARD therapy, less use of steroids and fewer medication changes after the initial visit.³¹

Combining and switching DMARDs

Anti-TNF therapy is recommended for the treatment of patients with RA after an inadequate response to traditional DMARDs. An inadequate response to DMARDs is defined as moderate to high disease activity despite treatment with at least 2 DMARDs (including MTX unless contraindicated) in monotherapy or combination therapy after 3 months at target dose. As shown in Figure 1, for patients who have failed treatment with 1 anti-TNF agent due to the lack of efficacy or toxicity, the following options are recommended: switch to another anti-TNF agent or switch to another biologic with a different mechanism of action (abatacept, rituximab or tocilizumab) or add MTX or another DMARD if the anti-TNF agent was used in monotherapy. In patients who have failed treatment with 2 anti-TNF agents, a switch to another biologic with a different mechanism of action (abatacept, rituximab or tocilizumab) is recommended.¹

Latent tuberculosis infection

The TNF inhibitors block an overexpressed signalling protein in RA, and in doing so, they also inhibit an important signalling protein in the normal immune response. The primary result is an increased risk of infection by both bacterial pathogens and atypical fungal and opportunistic pathogens.²⁰ TNF- α plays a central role in the host mechanism from tuberculosis (TB) in the formation of granulomas and containment of disease. Also, TB reactivation has been reported with all TNF inhibitors and is presumed to be a class effect, although some reports have suggested that the risk may be lower with etanercept.²⁰

Screening for latent TB infection is recommended prior to starting anti-TNF therapy, abatacept and tocilizumab. Screening should consist of history taking, including an assessment of latent TB infections, epidemiological risk factors, physical examination, tuberculin skin test and a chest radiograph in high-risk groups.¹

There is currently no "gold standard" for the diagnosis of latent TB infections. A tuberculin skin test performed according to the Mantoux

TABLE 1 DMARDs used to treat rheumatoid arthritis^{1,3,22,32,33}

DMARDs (traditional)			
Drug	Dose	Monitoring ^{1,22,32,33*}	Comments
MTX	Titrate to maximum dose of 25 mg weekly by rapid-dose escalation ¹ ; dose should be individualized; start oral or parenteral (consider switching to SC if inadequate response or intolerance to oral MTX) ¹	Baseline CBC, liver and renal biochemistry tests and chest x-ray required; screening for hepatitis B and C should be considered; HIV testing recommended in high-risk patients ¹ ; CBC, albumin, serum creatinine and LFT monthly for at least 6 months and then every 1-2 months thereafter ^{32,33} <u>Practice tip:</u> Do blood work the day prior to weekly MTX dose to reflect liver status at trough ²⁵	<u>Adverse effects:</u> <ul style="list-style-type: none"> • 24-72 hours after dose: nausea, malaise, flu-like aches, headaches, oral ulcers • Rarely: bone marrow and liver toxicity, pneumonitis <u>Contraindications:</u> <ul style="list-style-type: none"> • Pregnancy^{22†} • Patients with hepatitis B or C, renal insufficiency or lung disease <u>Drug interactions:</u> <ul style="list-style-type: none"> • Do not combine with trimethoprim (available as a single agent or combined with sulfamethoxazole [cotrimoxazole]) • Reported cases of pancytopenia due to additive antifolate effects^{17,19} <u>Practice tips:</u> <ul style="list-style-type: none"> • Give folic acid 5 mg weekly to control minor adverse effects (can give 5 mg 48 hours after MTX, preferably not on the same day as MTX) • Alcohol use: patient should discuss with rheumatologist • MTX can be self-administered SC using a 100 unit insulin syringe (29 or 30 gauge, 5/16 inch), which is safer to use than a 2-part tuberculin syringe (less chance of exposure if the needle disconnects from the tuberculin syringe) • 50 mg/2 mL vial with preservative is recommended for SC injection; prefilled syringes (Metoject) are more expensive than vials with concentration of 10 mg/mL • 2.5 mg tablet is preferred over 10 mg tablet for ease of dose titration
Hydroxychloroquine (Plaquenil, generics)	200-400 mg daily; tablets can be taken together or in split doses; can be taken with water on an empty stomach; to reduce nausea and vomiting (can be due to bitter taste), it can be taken with food or half an hour before bedtime ³⁴ ; daily dose should not exceed 6.5 mg/kg ideal (lean)	Baseline ophthalmological examination within first year of use; annual screening after 5 years of therapy ^{34,35} ; no routine blood monitoring required	Plaquenil brand is coated; other products may be bitter tasting <u>Adverse effects:</u> <ul style="list-style-type: none"> • Nausea, diarrhea, rash • Rarely: if dosed high for too long, corneal and retinal deposition can occur <u>Drug interactions:</u> <ul style="list-style-type: none"> • Avoid concomitant use of related medications such as quinine, chloroquine and mefloquine³⁶; avoid excessive intake of tonic water (up to 80 mg quinine/L)^{36,37}

TABLE 1 (continued)

DMARDs (traditional)			
Drug	Dose	Monitoring ^{1,22,32,33*}	Comments
	body weight/actual weight or 400 mg daily, whichever is less ¹³ ; exceeding the recommended daily dose increases the risk of retinal toxicity		<ul style="list-style-type: none"> • Avoid St. John's wort³⁸ • Hypoglycemia can occur; may benefit patients with diabetes with better glucose control; there is a case report of hypoglycemia in a patient without diabetes³⁹ <p><u>Practice tips:</u></p> <p>Benefits beyond inflammation reduction⁴⁰:</p> <ul style="list-style-type: none"> • Improves glucose profiles, lowers fasting insulin levels and lowers insulin resistance and hemoglobin A1C levels • Improves lipid profile, reduces low-density lipoprotein (LDL) and triglycerides and increases high-density lipoprotein (HDL) • Found to be thromboprotective in lupus • Benefits in lupus nephritis
Sulfasalazine (Salazopyrin, generics)	Initially 500 mg daily or twice daily orally; increase by 500 mg weekly to a maintenance dose of 2-3 g daily (divided in 2 doses)	CBC, LFT and serum creatinine at baseline and monthly for 3 months and then every 2-3 months or as clinically indicated ^{32,33}	<p><u>Adverse effects:</u></p> <ul style="list-style-type: none"> • Dose-related adverse effects: GI intolerance, headache • Hypersensitivity reactions (rash, fever), oligospermia (reversible), bone marrow toxicity (rare) • May cause sun sensitivity <p><u>Contraindications:</u></p> <ul style="list-style-type: none"> • Do not use if sulfa or salicylate allergy or G6PD deficiency <p><u>Drug interactions:</u></p> <ul style="list-style-type: none"> • Sulfasalazine may decrease absorption of digoxin <p><u>Practice tips:</u></p> <ul style="list-style-type: none"> • May cause orange-yellow discolouration of urine
Leflunomide (Arava, generics)	10-20 mg daily	Baseline hepatitis B and C serology; CBC, LFT and serum creatinine at baseline and monthly for 3 months and then every 2-3 months or as clinically indicated ^{32,33} ; LFTs should be monitored monthly if also taking MTX ¹	<p><u>Adverse effects:</u></p> <ul style="list-style-type: none"> • Nausea, diarrhea, anorexia, alopecia, hypertension, rash • May cause hepatotoxicity, cytopenia, profound anorexia and weight loss, pulmonary fibrosis, interstitial lung disease <p>Alcohol use: patient should discuss with rheumatologist</p> <p><u>Contraindications:</u></p> <ul style="list-style-type: none"> • Pregnancy[†] • Washout procedure with cholestyramine 8 g 3 times per day for 11 days is recommended for serious toxicity or imminently planned pregnancy <p><u>Practice tips:</u></p> <ul style="list-style-type: none"> • Loading dose often causes severe diarrhea and is no longer recommended • Blood pressure should be monitored at start of therapy

TABLE 1 (continued)

DMARDs (biologic)			
Drug and half-life	Dose	Monitoring*	Comments
TNF- α inhibitors (anti-TNF)			
Adalimumab (Humira): mean half-life of 14 days ³	40 mg SC every other week	As per CRA guidelines, ¹ prior to initiating all biologics: check CBC, LFT and serum creatinine and screen for hepatitis B and C (and HIV in high-risk patients); screen for latent TB prior to initiating anti-TNF, abatacept and tocilizumab; baseline antinuclear antibody testing could be considered prior to starting anti-TNF	<u>Adverse effects:</u> <ul style="list-style-type: none">• Injection site reactions, infections (including TB and opportunistic organisms), new-onset psoriasis, autoimmune phenomena• Increased risk of lymphoma (children and adolescents), leukemia and other malignancies <u>Contraindications:</u> <ul style="list-style-type: none">• Susceptibility to or presence of serious and/or recurrent infections• Consider lupus, demyelinating disease or heart failure as relative contraindications <u>Practice tips:</u> <ul style="list-style-type: none">• To improve response to antibiotic therapy, anti-TNF therapies should be held for the duration of antibiotic therapy• Adverse effects for infliximab include the class effects above and also infusion reactions• Heart failure if using more than 5 mg/kg per infusion
Certolizumab (Cimzia): mean half-life of 14 days ³	400 mg SC at weeks 0, 2 and 4 and then 200 mg every 2 weeks; may give 400 mg every 4 weeks SC as maintenance dose		
Etanercept (Enbrel): mean half-life of 4.3 days	25 mg SC twice weekly or 50 mg once weekly		
Golimumab (Simponi): mean half-life of 12 days	50 mg SC once monthly on same date each month		
Infliximab (Remicade): mean half-life of 8-10 days	3-5 mg/kg IV at weeks 0, 2 and 6 followed by every 4-8 weeks thereafter		
B cell depleters			
Rituximab (Rituxan): mean half-life of 21 days	1 g IV infusion given twice 2 weeks apart; infusions are given with 100 mg of methylprednisolone; retreatment can occur as early as 6 months if patient had initial response but has persistent synovitis	See anti-TNF class for monitoring ¹	<u>Adverse effects:</u> <ul style="list-style-type: none">• Mild to moderate infusion reactions• Very rare: progressive multifocal leukoencephalopathy <u>Contraindications:</u> <ul style="list-style-type: none">• Susceptibility to infections• Contraindicated in patients with known type 1 hypersensitivity or anaphylactic reactions to murine proteins, Chinese hamster ovary cell proteins or any component of the product
T cell costimulation inhibitors			
Abatacept (Orencia): mean half-life of 14 days (once monthly administration); mean half-life of 14 days (once weekly SC administration)	Dose based on weight; <60 kg: 500 mg IV initial infusion; 60-100 kg: 750 mg IV initial infusion; >100 kg: 1 g IV initial infusion; after initial infusion, administer at weeks 2 and 4 and then once monthly or abatacept 125 mg SC once weekly	See anti-TNF (above) ¹	<u>Adverse effects:</u> <ul style="list-style-type: none">• Rare minor infusion reactions <u>Contraindications:</u> <ul style="list-style-type: none">• Susceptibility to infections

TABLE 1 (continued)

DMARDs (biologic)			
Drug and half-life	Dose	Monitoring*	Comments
Interleukin-6 inhibitors			
Tocilizumab (Actemra): mean half-life of 13 days	4 mg/kg IV every 4 weeks infused over 1 hour; may increase to 8 mg/kg IV every 4 weeks if response is inadequate	See anti-TNF class; monitor for neutropenia, thrombocytopenia and elevated transaminases 4-8 weeks after starting therapy; may increase CYP450 enzyme activity, possibly reducing the bioavailability of some medications ⁴¹ ; monitor drugs metabolized by CYP450 for benefit	Adverse effects: <ul style="list-style-type: none"> • Infusion reactions, serious infections, GI perforation, decreased neutrophils, decreased platelets, increased lipids Majority of trials found no increase in adverse cardiovascular events; while these short-term efficacy and safety profiles are encouraging, further long-term safety data are required to better characterize the risk-benefit profile of tocilizumab ⁴²

CBC = complete blood count; CRA = Canadian Rheumatology Association; DMARD = disease-modifying antirheumatic drug; GI = gastrointestinal; IV = intravenous; LFT = liver function test; MTX = methotrexate; SC = subcutaneous; TB = tuberculosis; TNF = tumour necrosis factor.

This table was adapted with permission from Hazlewood G, Bykerk VP. Musculoskeletal disorders: rheumatoid arthritis. Available: www.etherapeutics.ca (accessed December 27, 2013). Also adapted from the CRA guidelines. Any additional information has been referenced.

*Monitoring includes information from e-Therapeutics, the CRA guidelines and the 2008 and 2012 American College of Rheumatology recommendations for the use of nonbiologic and biologic DMARDs in rheumatoid arthritis.^{32,33}

†For the most up-to-date recommendations on the use of any DMARD during pregnancy and breastfeeding, please consult MotherRisk at 1-877-439-2744 or www.motherisk.org/women/index.jsp.

TABLE 2 Websites and apps containing professional and patient educational information on rheumatoid arthritis

Website	Professional information	Patient teaching information
Canadian Rheumatology Association: www.rheum.ca	Recent information relevant to field of rheumatology; links to published guidelines	Not on this site
www.rheuminfo.com	Canadian site by rheumatologist Dr. Andy Thompson; helpful professional tools posted such as infusion protocols, prednisone reducing schedules, etc.	Patient medication and disease information in easy-to-read format including printable instructions on how to teach patients to self-inject methotrexate subcutaneously
The Arthritis Society (TAS): www.arthritis.ca	Research supported by TAS and professional educational programs	"Consumer Guide to Arthritis Medications 2011"; disease pamphlets
American College of Rheumatology (ACR): www.rheumatology.org	Look under Practice Management and then Clinical Support: Clinical Criteria for Rheumatic Diseases, Clinical Practice Guidelines, etc.	Patient resources (Medications and Disease) are under Clinical Support including ACR recommendations on medications used in pregnancy and breastfeeding
Arthritis Foundation (US): www.arthritis.org	Use the ACR site for professional US information	Canadian sites are more relevant; <i>Arthritis Today</i> magazine focuses on US health care
Ontario Rheumatology Association: www.ontariorheum.ca	Exceptional Access Program forms for biologics	Not available
Arthritis Consumer Experts: www.jointhealth.org	Biologic coverage/criteria across Canada	Patient information also available here
ArthritisID PRO: available through iTunes free of charge	Includes a screening tool, information on arthritis types including treatment and red flags, examination videos and continuing medical education credits	Companion app available for patient use
Hypertension Canada: www.hypertension.ca (updated annually)	Hypertension Canada provides both professional and patient information on how to properly take blood pressure and a Canadian list of recommended home blood pressure monitors	Home blood pressure monitors recommended by Hypertension Canada have a red heart/check mark logo on the box

FIGURE 1 Algorithm based on the Canadian Rheumatology Association recommendations for pharmacological treatment of rheumatoid arthritis with traditional and biologic disease-modifying antirheumatic drugs

Abbreviations: DMARD, disease-modifying antirheumatic drugs; MTX, methotrexate; anti-TNF, tumor necrosis factor inhibitor.

method is widely used in Canada. This test, however, has important limitations, including the potential for false-positive results in persons exposed to non-TB mycobacterial infections or those with a history of Bacille Calmette-Guérin (BCG) vaccinations and the potential for false-negative results in patients with RA receiving immunosuppressants or with comorbidities causing immunosuppression (e.g., cancer chemotherapy) or due to cutaneous anergy. Interferon- γ release assays are a more recent alternative to the tuberculin skin test. These assays may have reduced sensitivities in persons who do not have an intact immune system, are more costly (not covered by provincial plans) and are not widely accessible in Canada. Interferon- γ release assays may be an option to identify false-positive tuberculin skin test results in patients who received the BCG vaccine and have no epidemiological risk factors.³ A web-based tool

is available to help interpret a tuberculin skin test finding or interferon- γ release assay result (www.tstin3d.com/en/calc.html).

All patients who screen positive for latent TB infections should be offered prophylactic therapy in consultation with an infectious disease specialist as appropriate. In Canada, 9 months of prophylactic therapy with isoniazid is currently indicated as first-line therapy for those who screen positive for latent TB infections. Patients receiving isoniazid who are at risk for liver disease should be monitored at baseline and monthly for hepatotoxicity.²² The risk of hepatotoxicity has been reported to be lower with rifampin, although rifampin is considered as second-line therapy based on less long-term experience. Biologic agents may be started 1 to 2 months after the initiation of prophylaxis for latent TB infections.²

Practice Tip: Some rheumatologists and manufacturers of biologic DMARDs may provide

patients with wallet cards alerting physicians to atypical presentations of infections in patients taking biologic DMARDs. The warning cards usually explain that biologic use can increase the risk of serious opportunistic infections. It also cautions about the administration of any live vaccines to patients on biologic DMARDs. Ask your patients if they have such a card. If not, the pharmacist should encourage them to seek medical attention for any signs of infections and to consult with their rheumatologist prior to any vaccinations.

Vaccination

Patients with RA are at an increased risk of developing vaccine-preventable infections associated with significant morbidity and mortality. There are likely several factors contributing to this increased risk, including immune system dysfunction, comorbidities and/or use of immune-modulating therapies used to treat RA.

Vaccines can be either live attenuated or inactivated. Live-attenuated vaccines contain whole, living bacteria or viruses, which induce immunity by actively replicating within the host. Live vaccines should be administered at least 2 weeks and ideally 4 weeks before starting treatment with a biologic DMARD.³

It should be noted that the only live vaccine recommended in the guidelines for adults is the herpes zoster (shingles) vaccine for patients with RA who are 60 years or older. All other routine vaccinations that are recommended are killed or inactivated. The Public Health Agency of Canada provides up-to-date information on vaccines (including which are live or inactivated) in Canada at the following site: www.phac-aspc.gc.ca/publicat/cig-gci/p04-eng.php.

Inactivated vaccines contain killed bacteria or viruses. These vaccines may induce broad immunity because multiple antigens are present and pose no increased risk to immunocompromised persons.³ Vaccinations for influenza and pneumococcus are recommended for patients with RA before or during treatment with traditional and biologic DMARDs.³ A pneumococcal infection is one of the main pathogens for pulmonary infections, and patients with RA have been reported to be at an increased risk for pulmonary infections and resultant mortality.³ In the population with

RA, the intramuscular influenza vaccination, not intranasal (which is a live vaccine), is recommended annually. A hepatitis B vaccine should be considered in high-risk patient groups. A herpes zoster vaccine may be given to patients receiving MTX (≤ 25 mg/wk) and/or low-dose corticosteroids (< 20 mg/d).³

Practice Tip: With the increased mobility of patients and shortage of family doctors, pharmacists should encourage patients to maintain an up-to-date record of their vaccinations and review with them the adult vaccination recommendations in their province.

Malignancy

Patients with RA have been shown to have an overall slightly increased risk of malignancy, notably lung cancer and lymphoma, relative to the general population but a decreased risk for breast and colorectal cancers. The increased inflammatory burden in patients with RA is thought to contribute to an increased risk of lymphoma.³

In general, in patients with RA and active malignancy, treatment with traditional and biologic DMARDs should be delayed or withheld while patients are receiving chemotherapy or radiotherapy. However, systemic therapies administered to treat active malignancies may help achieve/maintain RA disease control, obviating the need for DMARD therapy.³ Refer to the CRA guidelines³ for a complete list of references up to 2011 for how to treat patients with RA who have malignancies.

The issue with data in this area is complex because cancer rates are low and have to be compared to patients with RA as a whole versus the general population. Also, clinical trials typically exclude patients with a history of malignancy. Thus, the creation of registries following large cohorts of real-world patients with RA is assisting with estimates of risks for several agents. While the data on anti-TNF agents are growing, the statistics on abatacept, rituximab and tocilizumab are still very limited at this time.²⁰

Practice Tip: Encourage patients to contribute to data collection when invited by their rheumatologist to participate in registries. For example, the Ontario Best Practice Research Initiative (www.obri.ca), formerly the Ontario Biologic Research Initiative, is a registry with the mission to improve the quality of care and health outcomes of patients

with RA by gathering long-term information on therapies, clinical practice and health care utilization in the real world.

Conclusion

There are many nonpharmacological and pharmacological options available to treat RA. The most important are early diagnosis, timely initiation of treatment and regular assessments to determine if treatment changes are required. The new CRA guidelines provide

recommendations for when to start treatment, what medications to use, the monitoring required and treatment options when RA remission or a state of low disease activity is not achieved.¹ Safety recommendations are also available with respect to perioperative care, latent TB infection, vaccination and treatment in patients with malignancy.³ These guidelines are a welcome addition to the pharmacist's resources for assisting with patient medication use and management of their RA condition. ■

From The Arthritis Program, Southlake Regional Health Centre, Newmarket, Ontario. Contact bornstein@bell.net.

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