Published in final edited form as:

Rheum Dis Clin North Am. 2018 August ; 44(3): 371–391. doi:10.1016/j.rdc.2018.03.010.

Pharmacotherapy Pearls in Rheumatology for the Care of Older Adult Patients: Focus on Oral Disease-Modifying Antirheumatic Drugs and the Newest Small Molecule inhibitors

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Abstract

Providing safe and effective pharmacotherapy to geriatric patients with rheumatological disorders is challenging. Multidisciplinary care involving rheumatologists, primary care physicians and other specialties can optimize benefit and reduce adverse outcomes. Oral disease-modifying antirheumatic drugs, including methotrexate, hydroxychloroquine, sulfasalazine, and leflunomide, and the small molecule inhibitors tofacitinib and apremilast have distinctive monitoring requirements and specific adverse reaction profiles. This article provides clinically relevant pearls for use of these interventions in older patients.

Keywords

Geriatrics; DMARDs; Rheumatology; Rheumatoid Arthritis; Tofacitinib; Apremilast

Introduction

Providing safe and effective pharmacotherapy to the geriatric patient population is an ongoing struggle for health care providers. The incidence of rheumatological disorders increases with advancing age. Recent National Health Interview Survey data (2013 – 2015) observed a prevalence of physician-diagnosed arthritis among adults aged 65 years and older approaches 50% with 44% of these patients having related activity limitation.¹ It is estimated that rheumatoid arthritis (RA) affects 0.5% to 1% of the adult population in

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The authors do not have any conflicts of interest related to this work.

developed countries. This translates to approximately 1.3 million Americans, with an increasing prevalence with advancing age.²

Oral disease-modifying antirheumatic drugs (DMARDs) are not only effective in reducing morbidity and improving quality of life but can also have a positive impact on mortality.³ However, DMARDs alter the host immune system and could create a risk of significant adverse events including infection and malignancy. A rheumatologist involved in the care of the elderly should be aware of specific adverse reactions and drug interactions associated with the use of oral DMARDs.

Older patients are at increased risk for adverse drug reactions. Budnitz and colleagues found individuals over the age of 65 were more likely than younger persons to have adverse drug reactions requiring emergency room visits and hospitalization.⁴ Such therapeutic misadventures in geriatric patients can be due to age-related changes in pharmacokinetics and pharmacodynamics, polypharmacy contributing to increased risk of clinically significant drug-drug interactions, and alterations in cognitive faculties that impair health literacy and therapeutic adherence.^{5–11} These problems are likely compounded by age bias, manifesting as a reluctance to aggressively treat older patients, as well as economic barriers.^{12,13} Management of rheumatologic conditions also carries special risk due to rapidly evolving use of novel therapeutic agents with limited data guiding their use in geriatric patients.

This review provides an update regarding commonly used oral DMARDs for the treatment of inflammatory arthritis, including methotrexate (MTX), hydroxychloroquine (HCQ), sulfasalazine (SSZ), and leflunomide, as well as the newer oral antirheumatic agents tofacitinib and apremilast. Although nonsteroidal anti-inflammatories, prednisone, and injectable biologic agents are commonly used in the management of inflammatory arthritis, these are outside the scope of this article.

Age-related changes in pharmacokinetics and pharmacodynamics

Pharmacokinetics is the study of drug absorption, distribution, metabolism, and excretion in the body. Geriatric patients experience physiologic changes at every step of the pharmacokinetic process.^{7,9} However, understanding of the age-related changes on pharmacokinetic properties of particular medications has been hampered by the general lack of inclusion of older adults in clinical trials and drug-specific pharmacokinetic studies. The most clinically significant pharmacokinetic alteration in the geriatric population is a decline in renal function that decreases metabolite excretion. Several commonly used anti-rheumatic medications, such as MTX, require monitoring of renal function.

Pharmacodynamics is the study of the biochemical and physiologic effects of drugs in the body. The pharmacodynamic changes with aging are more difficult to study and less characterized than pharmacokinetic alterations. In general, the response in elderly is less predictable and subject to more interindividual variability.¹¹ Aging patients experience changes at multiple levels including receptor, signal transduction or homeostatic mechanisms. This can not only affect the effectiveness but also the risk of adverse reactions. For example, a decrease in cell density and cell proliferation in the bone marrow in elderly

individuals,⁷ can make these patients especially sensitive to the hematological side effects of MTX.

Polypharmacy

Polypharmacy has been defined in many ways. Some definitions focus on the number of medications whereas others consider clinical appropriateness and indication.^{10,14–16} Consequences to polypharmacy include the risk for clinically significant drug-drug interactions, adverse drug reactions, and nonadherence.¹⁰

Age is an important risk factor for polypharmacy.¹⁴ Geriatric patients receiving multiple medications are at increased risk for cognitive impairment, falls, incontinence, and poor nutritional status.¹⁰ The complex medical regimens of RA place older patients at such risks. Treharne and colleagues¹⁷ found that the total number of RA medications was predicted by advancing age and longer disease duration. In addition, the total number of comorbidities contributed to this relationship. A 2001 study of hospitalized subjects with rheumatic diseases also found similar results, with older subjects having a higher likelihood of meeting the study's definition of polypharmacy compared with younger subjects.¹⁸

Health literacy

Health literacy, defined as an individual's overall capacity to obtain, process, and understand basic health information and services needed to make appropriate health decisions, is another area in which age-related changes may have an impact.¹⁹ Wong and colleagues noted that a third of patients prescribed common rheumatology medications followed the dosing instructions incorrectly.²⁰ Several studies have found a relationship between older age and reduced health literacy. This relationship may be influenced by the educational level and age-related changes to functional status, such as visual impairment.^{5,21–23} One study identified age older than 55 years as a risk factor for poor knowledge of MTX use in a diverse urban rheumatology clinic population in California.²⁴

Age bias

Older patients may face yet another challenge in receiving safe and effective treatment of rheumatological disorders in the form of age bias, or disparities in the prescription of treatment by doctors based on patient age.^{13,25,26} In a 2010 choice-based conjoint analysis, Kievit and colleagues showed that among 135 rheumatologists, patient's age was an important factor in the decision to escalate RA treatment.¹² Tutuncu and colleagues found that patients with older-onset RA were less frequently treated with biologic drugs and combination DMARDs than those with younger-onset RA, even though they had comparable disease severity and activity.²⁷ The reluctance to escalate therapy may result in older patients not receiving appropriate interventions, despite evidence of similar responsiveness to standard therapies when compared with younger patients.²⁸

Due to these complexities, rheumatologists, working in partnership with other members of the allied health care team, can most effectively minimize the risk for therapeutic misadventure.

DMARD and the Risk of Infection

Autoimmune disease itself is a risk factor for infection. Patients with RA were found to have a higher risk of infection, when compared to controls with no RA.²⁹ Addition of immunosuppressive and immunomodulatory agents for the treatment of autoimmune disease further increase the risk of infection. In a systemic literature review of observational studies and RA registries, the risk of serious infections was found to be higher among patients on biologic DMARDs (bDMARDs) compared to the conventional synthetic DMARDs (csDMARDs), with a hazard ratio (HR) ranging from 1.1 to 2.4. The risk of tuberculosis was also significantly higher among patients on bDMARDs compared to the general population (HR: 34.9 [8.9, 137.2]) and when compared with patients on csDMARDs (HR: 12.5 [3.5, 44.7]).³⁰ As with other DMARDs, risk of infection is a concern with the targeted synthetic DMARD (tsDMARD), tofacitinib. Pooled data from multiple phase 2, phase 3 and long-term extension studies of tofacitinib for RA found that the overall incidence rate of serious infections was 3 events per 100 patient-years. Pneumonia, herpes zoster, urinary tract infection and cellulitis were the most common. The incidence rates were found comparable to other bDMARDs (3.0 to 5.5 per patient-years) and TNF inhibitors (3.2 to 4.6 per patient-years). The incidence of infection did not increase with longer duration of tofacitinib use and was stable over time. The risk factors independently associated with increased risk of serious infection were: age more than 65, corticosteroid use (>7.5mg), diabetes and tofacitinib dose.³¹ Adequate vaccination of patients with rheumatological disease is the key strategy in preventing infectious complications. Hence the Advisory Committee on Immunization Practices (ACIP) has recommended vaccination of patients with chronic inflammatory disease on immunosuppression with Pneumococcal Vaccines (PCV-13 followed by PCV-23) and annual influenza vaccine.³²

Methotrexate

MTX is the most common DMARD used to treat RA and remains the cornerstone of treatment for this condition. The therapeutic effect of MTX in inflammatory arthritis was first reported in the 1950s,^{33,34} but did not receive Food and Drug Administration (FDA) approval for the treatment of RA until 1988. It is also used to treat several other rheumatic conditions such as juvenile idiopathic arthritis,^{35,36} psoriatic arthritis,³⁷ reactive arthritis,³⁸ systemic lupus erythematosus,³⁹ granulomatosis with polyangiitis,⁴⁰ and polymyositis/dermatomyositis.⁴¹

The exact mechanism by which MTX exerts its therapeutic effects in RA is not fully understood. MTX is a folate analogue that enters the cells primarily mediated by folate transporter 1 (FOLT), also known as reduced folate carrier 1 (RFC1). Once inside the cells, MTX undergoes polyglutamation catalyzed by folylpolyglutamate synthetase in the same manner as naturally occurring folate. MTX polyglutamates (MTX-glu) increase both the retention of MTX in the cells as well as its inhibitory actions in several intracellular enzymes. First, MTX inhibits dihydrofolate reductase (DHFR), the enzyme required for reduction of dihydrofolate (FH2) to tetrahydrofolate (FH4), resulting in suppression of purines, thymidylate, serine, and methionine synthesis, and ultimately, DNA production. Second, MTX inhibits thymidylate synthetase (TYMS), an enzyme that converts

deoxyuridine monophosphate (dUMP) to deoxythymidine monophosphate (dTMP), ultimately leading to decreased levels of pyrimidine that would be required for DNA biosynthesis. Finally, inhibition of 5-aminoimidazole-4-carboxamide ribonucleotide (AICAR) transformylase (ATIC) initiates a series of events that results in increased adenosine levels, which has multiple anti-inflammatory effects. For example, adenosine is associated with a decreased production of proinflammatory cytokines, such as tumor necrosis factor alpha (TNF α) and interleukin (IL)-6, as well as increased production of anti-inflammatory cytokines such as IL-10. It appears that adenosine, acting on adenosine receptors, is itself a key mediator of the anti-inflammatory effect of MTX whereas the inhibition of DHFR and TYMS seems to contribute more to antiproliferative effects.^{42–44}

In the mid-1980's, four clinical trials in patients with active RA showed that MTX was superior to placebo in decreasing disease activity in the short-term.^{45–48} Since then, MTX has been clearly established as a mainstay in the therapy of RA. A systematic review of 7 randomized, placebo-controlled trials (n=732 patients) in RA showed that MTX (doses between 5 mg and 25 mg weekly) was associated with a clinically important and statistically significant improvement in the American College of Rheumatology (ACR) 50 response rate at 52 weeks when compared with placebo (relative risk [RR] 3.0, 95% confidence interval [CI] 1.5 to 6.0). Radiographic progression rates were significantly lower in the MTX-treated group compared with the placebo group (RR 0.31, 95% CI 0.11 to 0.86) but no significant differences were observed in radiographic scores.⁴⁹ A 2016 network meta-analysis (158 trials, more than 37,000 patients) showed that the combination of MTX, SSZ, and HCQ (i.e., triple therapy) was superior to MTX for ACR50 response and was not statistically different from MTX plus any biologic or tofacitinib in patients with no previous MTX use or with inadequate response to this medication.⁵⁰ The 2015 ACR guideline for the treatment of RA has recommended the use of MTX as a preferred initial DMARD for most RA patients and to serve as the anchor drug in combination with biological therapy.⁵¹

In rheumatic conditions, MTX is prescribed as a low-dose regimen (typically dosed 25 mg weekly). It can be administered once weekly via oral, subcutaneous, or intramuscular route. There is no difference in the bioavailability of intramuscular versus subcutaneous route of administration,⁵² but the former is not frequently used. Oral bioavailability varies broadly among patients and decreases with increasing dose. A phase 2 study that evaluated the relative bioavailability of oral vs. subcutaneous MTX, showed that systemic exposure of oral MTX plateaued at doses 15 mg weekly, whereas subcutaneous administration at the same dose resulted in linear increases in systemic exposure. Hence, subcutaneous injection at higher doses is an alternative approach that can improve bioavailability.⁵³ Another strategy to improve the bioavailability of oral administration includes splitting of the dose of MTX, such as giving one-half dose repeated 12 hours apart on the same day, once weekly. The efficacy of MTX dose splitting has only been addressed in limited studies.⁵⁴

MTX is well tolerated in most RA patients. In a 2014 systematic review of 7 placebo-controlled trials, the adverse event rate at 12 weeks in the MTX monotherapy group was 45% (vs. 15% in the placebo group; RR 3.0, 95% CI 1.4 to 6.4) and MTX was associated with a higher rate of discontinuation due to adverse events compared to placebo (16% vs. 8%; RR 2.1, 95% CI 1.3 to 3.3).⁴⁹ Another review of 21 prospective studies (2009) found

that the long-term therapy (>2 years of treatment; n=3463 patients) with MTX was associated with frequent adverse reactions (73%) but they were generally mild and caused discontinuation in around 11% of the patients.⁵⁵

The most common adverse reactions of MTX are gastrointestinal (nausea, vomiting, abdominal pain, diarrhea and stomatitis), elevated hepatic enzymes, dermatological (skin rash, pruritus, and alopecia), neurological (headache, vertigo, lethargy, and cognitive dysfunction), hematological (cytopenia), and pulmonary (such as pneumonitis). The rate of toxicity increases in patients with renal impairment.⁵⁶ MTX is eliminated primarily via renal excretion and may accumulate in the setting of reduced renal function.^{57,58} Elevated liver enzymes are frequent adverse reactions and an important reason for treatment withdrawal. It occurs in up to 20% of patients and leads to discontinuation in 4% of patients during long-term use.⁵⁵ Although, these events are usually self-limited, they can potentially lead to liver cirrhosis.⁵⁹ Risk factors for liver injury during MTX therapy are alcohol use, history of liver disease (e.g., hepatitis B or C), other comorbidities (diabetes, obesity, hyperlipidemia), exposure to hepatotoxic medications, lack of folate supplementation, persistent abnormal liver panel, and family history of heritable liver disease.⁶⁰

Several measures can be used to decrease adverse reactions associated with MTX. Laboratory monitoring for MTX toxicity should start with determining baseline complete blood cell counts, liver enzymes, and serum creatinine level; and thereafter followed by monitoring at regular intervals.⁵¹ Folic acid or folinic acid supplementation may ameliorate some of the folate-pathway-dependent adverse effects, including hematologic, gastrointestinal and hepatic side effects.⁶¹ Switching from oral to parenteral route therapy or splitting the dose of MTX are other strategies that have been recommended albeit with limited scientific support.⁶²

Few elderly patients were included in the initial trials with MTX but accumulating data over time has helped to better understand MTX in this population. The efficacy response of geriatric patients with active RA to MTX treatment is comparable to that of younger patients.²⁸ Given the safety profile of this medication, extra caution must be exercised when treating geriatric patients. A decline in renal function may be associated with impaired clearance and increased toxicity of MTX,^{56–58} which is particularly relevant in the elderly. Close monitoring for signs of hepatic and hematologic toxicity should be emphasized as well.

Elderly patients are vulnerable to clinically significant drug interactions with MTX. Trimethoprim-sulfamethoxazole (TMP-SMX), a commonly prescribed antibiotic with folate antagonist effect, can increase the occurrence of hematologic manifestations and life-threatening pancytopenia. In a 2010 systematic review of 67 articles addressing MTX-drug interactions,⁶³ cytopenia and elevation of liver enzymes were the main reported toxicities. In this review, clinically significant interactions with TMP-SMX therapy were noted in one observational study and in 17 case reports. TMP-SMX was mostly indicated for urinary tract infections. There were no reported cases of toxicity with use of prophylactic doses of 3 times per week. High-dose aspirin was also found to exacerbate the toxicity of MTX.⁶³ Other drugs known to cause hepatotoxicity such as SSZ, leflunomide, and azathioprine may

increase the incidence of liver toxicity when used in combination with MTX.⁶⁴ Because MTX can accumulate in the setting of reduced clearance, medications that affect renal function should be avoided or used with caution (Box 1).

Hydroxychloroquine

HCQ is another commonly used DMARD for the management of rheumatological disorders. The precise mechanism of action of HCQ is unknown but is thought to have immunomodulatory and anti-inflammatory activity through stabilization of the lysosomal membrane, down-regulation of antigen presentation and inhibition of cell-mediated cytotoxicity.⁶⁵ It also interferes with the innate immune response by inhibiting the Toll-like receptors (TLR)⁶⁶.

HCQ carries FDA approval for the treatment of RA and systemic lupus erythematosus (SLE). In RA, it is best used in mild, early disease or as a component of combination therapy. Treatment with HCQ was found to be an independent determinant of remission in RA in a multicenter cross-sectional study. HCQ has exhibited synergistic effects in improving disease activity when used in combination with other DMARDs, including MTX and SSZ (triple therapy).^{67,68}

The use of HCQ is well established in cutaneous forms of SLE. In a comparative study of HCQ and acitretin, there was similar clinical efficacy, with 50% of the patient having a complete resolution of discoid lupus.⁶⁹ HCQ is beneficial in the management of non-organ threatening disease manifestations including arthralgia, fatigue, fever, and rash. In SLE patients, it has been demonstrated to decrease the risk of flare⁷⁰, decrease the risk of thromboembolism in patients with antiphospholipid antibodies,⁷¹ lower total cholesterol in patients taking steroids,⁷² and lower fasting blood glucose concentration.⁷³ HCQ was also shown to have a beneficial effect on the survival of lupus patients⁷⁴ and a protective effect on the risk of organ damage.⁷⁵

HCQ is generally regarded as well tolerated, with gastrointestinal distress being the most common adverse effect. Skin hyperpigmentation is also a known side effect of long-term HCQ therapy. HCQ-induced blue-black dyschromia has been clinically misinterpreted as elder abuse. These cases were resolved after a thorough history or, in some cases, a skin biopsy.^{76,77}

Post-marketing cases of cardiomyopathy and QT interval prolongation have been reported with the use of HCQ. Other rare adverse events reported include hypoglycemia, proximal myopathy and neuropathy. For this reason, caution is recommended when co-administering with hypoglycemic agents or medications with arrhythmic potential.⁷⁸

HCQ has the potential to cause irreversible retinal toxicity. A 2014 retrospective case-control study reviewed more than 2300 patient records of HCQ users with at least 5 years of treatment duration in a large integrated health organization of 3.4 million overall members. The overall prevalence of HCQ-related retinopathy was reported to be 7.5%, with risk dependent on dosage and duration of use. Patient on more than 5 mg/kg had 10% risk within 10 years of use and a 40% risk after 20 years of use. In patients using less than 5 mg/kg, the

risk was reduced to 2% within the first 10 years and 20% after 20 years of use. Other risk factors for retinopathy include renal disease (GFR < 60ml/minute) or concurrent use of tamoxifen. Notably, age was not identified as a risk factor.⁷⁹ Based on these data, the American Academy of Ophthalmology has recommended a maximum daily dosing of less than 5 mg/kg real body weight and a baseline fundus examination to rule out preexisting maculopathy. In patients with no major risk factors, the annual screening should be done after 5 years of HCQ use. The recommended modalities of screening are visual fields and spectral-domain optical coherence tomography (SD-OCT).⁸⁰ (Box 2)

Sulfasalazine

SSZ is a well-established DMARD that is most commonly used as a second-line agent in RA combination therapy but is also indicated to treat other inflammatory arthritides and inflammatory bowel disease. SSZ is composed of sulfapyridine and 5-aminosalicylic acid and it is thought that the antiarthritic activity of this compound is mostly conferred by the sulfapyridine moiety. The precise mechanism of action of SSZ is not elucidated but may involve several anti-inflammatory and immunomodulatory effects such as inhibition of proinflammatory cytokines (e.g., TNF- α and IL-8) and increase of adenosine release at inflamed sites (similar to MTX).^{81–83}

Genetic polymorphisms may play a role in the efficacy of the drug as well as the propensity for adverse effects. A prolonged half-life and accumulation of the sulfapyridine metabolite of SSZ with a subsequent increase in toxicity may be seen in slow acetylators.⁸⁴ Patients with glucose-6 phosphate dehydrogenase (G6PD) deficiency are at increased risk of hemolytic anemia after initiation SSZ treatment.⁸⁵

Although it may be used alone, SSZ is typically prescribed with MTX and HCQ as part of so-called RA ‘triple therapy’. SSZ is the most commonly discontinued drug in this regimen secondary to adverse effects.⁸⁶ It is associated with gastrointestinal, central nervous system (headache, dizziness), cutaneous, and hematologic adverse reactions. The gastrointestinal complaints are usually mild in nature. They resolve with discontinuation or dose reduction and are better tolerated with the use of an enteric-coated formulation.^{87,88}

A syndrome of fever, rash, and abnormal liver tests can occur in the setting of SSZ therapy. In the presence of eosinophilia, this reaction is termed drug rash with eosinophilia and systemic symptoms (DRESS).⁸⁹ Finally, a rare adverse effect of SSA is crystalluria with intra-tubular precipitation of sulfasalazine metabolites, and subsequent acute kidney injury.^{90,91} Therefore, vigilance toward maintaining adequate hydration and monitoring renal function is prudent in older individuals treated with SSZ (Box 3).

Leflunomide

Leflunomide is an isoxazole derivative that inhibits dihydroorotate dehydrogenase in the pyrimidine pathway. T lymphocytes are dependent on the de novo synthesis of pyrimidine. Decreased pyrimidine leads to decreased T cell proliferation. Leflunomide is also known to modulate T-cell immunology by shifting the T-helper (Th)1/Th2 balance.⁹² Consequently, it has successfully been used in the treatment of various inflammatory arthritides. It received

FDA approval for use in RA in 1998. There are no large head to head randomized clinical trials comparing leflunomide with MTX, but the available evidence suggests a comparable clinical efficacy⁹³. The use of leflunomide is limited by the lack of enough evidence for its use in combination with other biological DMARDs.

Leflunomide has a similar safety profile as MTX. The most common reactions include gastrointestinal upset, hepatotoxicity, alopecia, and risk of infection.⁹³ Adverse events are similar regardless of patient age.⁹⁴ Safe prescribing of this agent relies on monitoring not only the blood count and liver function but also blood pressure. In a long-term study in patients with RA treated with leflunomide, clinically relevant increase in blood pressure was found in 5% of the patients but in most cases normalized during ongoing treatment.⁹⁵ Leflunomide is also associated with significant but modest weight loss compared to other RA medications.⁹⁶ In a small study of patients with RA treated with leflunomide, significant weight loss was found in 5 out of 70 patients (7%) and the weight loss ranged from 19 to 53 pounds (14%–26% decrease from baseline). Most patients had weight loss early (within 6 months) of initiation of the medication and on further continuation of medication the weight stabilized.⁹⁷ Hepatotoxicity is an important adverse reaction of leflunomide and cases of severe liver injury have been reported; therefore, it is not recommended to use in patients with preexisting liver disease.⁹⁸

Due to low hepatic clearance and enterohepatic recycling, the pharmacokinetic profile of leflunomide is notable for a long elimination half-life of approximately 2 weeks.⁹⁹ In the setting of severe toxicity or other condition necessitating rapid withdrawal, cholestyramine can be used to bind the active metabolite of leflunomide in the intestine and interrupt enterohepatic or entero-entero recycling, thus reducing the half-life to 1 to 2 days.^{99–102} (Box 4)

Janus Kinase Inhibitors

Janus kinase inhibitors are synthetic DMARDs that target the janus kinase (JAK) and signal transducer and activator of transcription (STAT) intracellular signaling pathway. The JAK/STAT pathway mediates intracellular signaling in a variety of ways. The JAK1-JAK3 complex is involved in lymphocyte proliferation induced by interleukins such as IL-2, IL-4, IL-7, IL-9, IL-15, and IL-21. The JAK 2 homodimer is essential in intracellular signaling by erythropoietin and granulocyte-macrophage colony stimulating factor, which is required for erythropoiesis, myelopoiesis, and thrombopoiesis.¹⁰³ The JAK-STAT pathway is also involved in the host immune response against viral infection and mycobacterial infection.

Tofacitinib is a JAK inhibitor, which is FDA approved for the treatment of RA. It inhibits JAK1 and JAK3, but also inhibits JAK 2 to a lesser degree.¹⁰⁴ It is indicated for the treatment of adult patients with moderate to severe RA with inadequate response or intolerance to MTX.^{105–108} It may be used as monotherapy or in combination with MTX or other DMARDs. Tofacitinib is also approved for active psoriatic arthritis. Trials are currently underway studying the agent's effects in the management of other disease states, including juvenile idiopathic arthritis, SLE, psoriatic arthritis, and ankylosing spondylitis.

Tofacitinib is FDA-approved for daily dosing at 5 mg twice daily or with the extended-release formulation at 11 mg once daily. Tofacitinib is metabolized via cytochrome P450 (CYP) 3A4 and a lesser degree via CYP2C19. Strong inhibitors of CYP 3A4 increase the effect of tofacitinib, increasing the toxicity whereas inducers of CYP3A4 decrease the effect of tofacitinib (Table 1).

Herpes zoster infection is a concern in geriatric RA patients on tofacitinib. Older age is one of the most important risk factors for the development of herpes zoster infection.¹¹³ In addition, RA is an independent risk factor for herpes zoster (adjusted hazard ratio = 1.9 [95% CI = 1.8–2.0]).¹¹⁴ In phase II, phase III and long-term extension studies, the incidence rate of herpes zoster was found higher among the tofacitinib group compared to the placebo (crude incidence rate of 4.4 per 100 patient-years [95% CI 3.8–4.9]) and was more common among Japanese and Korean patients. Not surprisingly, older age was associated with higher risk (odds ratio 1.9, 95% CI 1.5–2.6). Among the patients with herpes zoster, 7% of them had serious disease requiring hospitalization or use of intravenous antiviral treatment.¹¹⁵ The risk of herpes zoster infection was found to be higher in patients taking tofacitinib in combination with glucocorticoids compared to those on monotherapy with only tofacitinib.¹¹⁶ These studies underscore the importance of adequate vaccination before initiation of tofacitinib. The 2015 ACR guideline for the treatment of RA has recommended the administration of herpes zoster vaccine before starting biologic or tofacitinib in RA patients ages 50 years. After vaccination, they recommended a 2-week waiting period before starting a biologic.⁵¹ The Infectious Disease Society of America (IDSA) has recommended administration of live vaccine greater than or equal to 4 weeks before the use of immunosuppressive agents.¹¹⁷ Despite the safety and benefit of this approach, vaccination against herpes zoster is woefully underutilized in patients with RA.¹¹⁸ A new recombinant zoster vaccine (brand name, Shingrex) was recommended by ACIP in 2017 for immunocompetent patients above the age of 50 years. The vaccine is recommended at day 0 with a repeat dose after 2 months.¹¹⁹ This vaccine is found to be more efficacious and reduces the risk of herpes zoster and post-herpetic neuralgia by more than 90%.¹²⁰ Due to the inactivated nature of the vaccine, it could be administered 2 weeks prior to the initiation of tofacitinib and this strategy could potentially mitigate the underutilization of such vaccination.

Winthrop and colleagues illustrated a diminished responsiveness to the 23-valent pneumococcal polysaccharide vaccine (PPSV-23) in subjects commencing tofacitinib therapy at a dose of 10 mg twice daily. The response was further diminished in subjects with concomitant MTX. However, the response to annual influenza vaccination was unaltered in subjects receiving tofacitinib, with or without MTX. For current users, a 2-week holiday from tofacitinib around the time of vaccination did not appreciably improve immunogenicity for the PPSV-23 vaccine. Although most users developed sufficient responses to both vaccines, administration of the pneumococcal vaccine before initiation of tofacitinib may improve overall response and should be considered (BOX 5).¹²¹

Apremilast

Apremilast is an oral small molecule that belongs to a class of new drugs known as phosphodiesterase-4 (PDE4) inhibitors. It was approved by the FDA for the treatment of psoriasis and psoriatic arthritis. PDE-4 is a superfamily of enzymes that catalyze the hydrolysis of cyclic adenosine monophosphate (cAMP).¹²² Inhibition of PDE4 increases the levels of cAMP, a well-known intracellular second messenger that leads to activation of cAMP-dependent protein kinase A (PKA). This causes modifications of several transcription factors such as the activation of cAMP-response element binding protein (CREB) and inhibition of nuclear factor kappa B (NF- κ B).^{123,124} The specific mechanism of action by which apremilast exerts its therapeutic effects remains incompletely understood but it is known to modify the production of several cytokines, presumably enhancing cAMP actions at the transcriptional level. PDE4 inhibition reduces secretion of pro-inflammatory cytokines such as TNF α , IFN γ , and IL-2; and increases production of anti-inflammatory modulators such as IL-10.^{125,126}

The efficacy and safety of apremilast for the treatment of psoriatic arthritis has been evaluated in four randomized, double-blinded, placebo-controlled phase 3 trials in the Psoriatic Arthritis Long-term Assessment of Clinical Efficacy programme (PALACE 1–4 trials).^{127–131} Patients were randomized to receive apremilast 20 or 30 mg twice daily or placebo. PALACE 1–3 enrolled a total of 1493 patients with active psoriasis arthritis despite prior traditional DMARD or biologic treatment. PALACE 4 included 527 patients with no prior DMARD or biological therapy. The primary endpoint was the ACR20 response rate at week 16 and the key secondary endpoint was the change from baseline in the Health Assessment Questionnaire-Disability Index (HAQ-DI) score at week 16. Apremilast improved signs and symptoms in patients with active psoriatic arthritis when compared to placebo. At week 16, the ACR20 response rate was significantly higher with apremilast 30 mg twice daily than with placebo across all trials (40 vs. 19% in PALACE 1, 32 vs. 19% in PALACE 2, 41 vs. 18% in PALACE 3, and 31 vs. 16 in PALACE 4). Improvements in HAQ-DI were also seen with apremilast in PALACE trials. For example, in PALACE 1 the mean changes from baseline at week 16 were –0.09 (standard error 0.04) in the placebo group and –0.25 (0.04) in apremilast 30 mg BID ($p=0.0015$ vs. placebo) in the per protocol population. Compared to placebo, a significantly greater proportion of patients receiving apremilast 30 mg BID achieved minimal clinically important differences (MCID) of 0.13 (39% placebo vs. 50% apremilast 30 mg BID; $p=0.0334$) and 0.30 (27% placebo vs. 40% apremilast 30 mg BID; $p=0.0149$) as measured by the HAQ-DI at week 16. This efficacy was sustained and the benefit of apremilast in psoriatic arthritis has been reported in extensions up to 4 years of treatment.¹³²

The efficacy and safety of apremilast in active psoriatic arthritis was also evaluated in a phase 3B, randomized, double-blind, placebo-controlled trial (ACTIVE trial).¹³³ Patients ($n=219$) who may have had one prior conventional therapy and were not previously treated with a biological agent were randomized to apremilast 30 mg twice daily ($n=110$) or placebo ($n=109$) for 24 weeks. A significantly greater ACR20 response at week 16 (primary outcome) was observed with apremilast versus placebo (38% vs. 20%; $P=0.004$). This trial also assessed the onset of apremilast efficacy at earlier time points (beginning at week 2)

than in previous studies. At week 2 (first assessment), response rates were 16% in apremilast group versus 6% ($P=0.025$) in the placebo group. Improvements in other manifestations, including swollen and tender joints, enthesitis, physical impairment and morning stiffness severity, were also observed with apremilast at week 2. The benefit was maintained with continued treatment through week 52.

Apremilast has an acceptable safety profile and, in general, is well tolerated. The most frequent adverse reactions are diarrhea, nausea, upper respiratory tract infection, and headache. The gastrointestinal manifestations are the most common reactions and typically are mild or moderate in severity, occur early in therapy, and resolve with continued treatment.^{127–129} In the PALACE 1, the frequency of the most common adverse events reported with apremilast 30 mg BID ($n=168$) in the placebo-controlled phase (weeks 0–24) were diarrhea (19.0%), nausea (18.5%), headache (10.7%), and upper respiratory tract infection (4.2%).¹²⁷ Weight loss has also been reported (5% to 10% of body weight loss in 10% to 12% of subjects; 10% of body weight loss in 2%). Therefore, it is recommended to monitor weight regularly in patients treated with apremilast, and consider discontinuation if unexplained or clinically significant weight loss occurs. Apremilast is also associated with an increase in reports of depression. Hence the risks and benefits of this medication should be weighed in patients with a history of depression or mood changes.¹³⁴ Treatment with apremilast is not associated with clinically meaningful laboratory abnormalities and routine laboratory monitoring is not required. However, baseline serum creatinine is important because the dose should be reduced to 30 mg once daily in patients with an estimated creatinine clearance less than 30 mL/min. In a pooled safety analysis of three trials (PALACE 1, 2, and 3), no new safety concerns were identified with long-term exposure over 52 weeks.¹³⁵

The acceptable safety profile of apremilast makes this drug an appealing therapeutic option for geriatric patients. Of the total number of patients with psoriatic arthritis who enrolled in PALACE 1–3, around 10% (146 out of 1493) were ≥ 65 years of age. No overall differences were obtained in the safety profile of this age group compared with the younger group in the clinical studies. Similar results were obtained in the clinical trials of apremilast in psoriasis. In the Efficacy and Safety Trial Evaluating the Effects of Apremilast in Psoriasis (ESTEEM 1 and 2) phase III clinical trial program,^{136,137} about 9% (108 out of 1257) of the subjects who enrolled were ≥ 65 years of age. No overall differences were observed in the efficacy and safety in patients ≥ 65 years of age and younger patients.¹³⁴

The clinical use of apremilast has also been explored in other rheumatic and dermatological conditions including RA, Behçet's disease, and different forms of dermatitis.¹³⁸ In RA, a phase 2, randomized, placebo-controlled trial in patients with active arthritis who had an inadequate response to MTX failed to meet the primary efficacy endpoint.¹³⁹ Further studies are needed to clarify the radiographic effect in psoriatic arthritis and to determine the actual therapeutic role compared to conventional DMARDs and biologics (Box 6).

Summary

An effective treatment strategy targeting rheumatological disorders in the elderly should be directed at maximizing the quality of life. In patients with RA, a treat-to-target approach with the goal of remission or low disease activity has improved outcomes.¹⁴⁰ However, treatment in geriatric patients is challenging because they are particularly vulnerable to adverse reactions. Factors known to increase this risk for adverse reactions include age-related changes in pharmacokinetics and pharmacodynamics, comorbidities, polypharmacy, and drug compliance issues. Moreover, pharmacotherapy in rheumatology is evolving rapidly while guidance on how to apply the new advances to older individuals is frequently missing. Regular monitoring of clinical and laboratory parameters that is tailored to the specific medication and the comorbidities is crucial to minimize negative outcomes. Finally, educating the patient or caregiver and involving them in making decisions and setting the treatment goals is paramount to ensure an optimal outcome.

Acknowledgments

Disclosure Statement: This work was supported by the Intramural Program of the National Institute of Arthritis and Musculoskeletal and Skin Diseases of the National Institutes of Health. This article reflects the views of the authors and should not be construed to represent FDA's views or policies.

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Box 1. Clinical pearls: MTX

- Monitor renal function; dose adjust accordingly.
- Folic acid or folinic acid supplementation can improve tolerability of MTX.
- Avoid concomitant use of TMP-SMX when dosed daily.

Box 2. Clinical pearls: HCQ

- HCQ is a mainstay in the management of skin manifestations caused by SLE.
- Judicious dosing to avoid toxicity should be practiced using a 5.0 mg/kg actual body weight cutoff.
- Routine ophthalmology examinations are recommended to screen for the development of retinal toxicity.

Box 3. Clinical pearls: SSZ

- Initiation therapy with a gradual dose increase and interval laboratory monitoring can minimize the risk of adverse reactions.
- Slow acetylators and patients with G6PD are at increased risk of toxicity.
- Crystalluria is a rare adverse effect. Patients should maintain adequate hydration.

Box 4. Clinical pearls: leflunomide

- Hypertension and unintentional weight loss are two adverse effects related to leflunomide therapy that may be of particular concern in older patients.
- Regular monitoring for hepatotoxicity is recommended.
- In the clinical scenarios requiring rapid withdrawal of leflunomide, a cholestyramine washout can be implemented to decrease the half-life of the active metabolite.

Clinical pearls: tofacitinib

- Tofacitinib is a new and effective treatment option for RA, which could be used with or without MTX.
- Patients should receive screening for tuberculosis before therapy initiation.
- Risk of infections including herpes zoster may be higher in patients receiving tofacitinib, specifically Asian patients.
- Tofacitinib therapy may blunt the immune response to specific vaccines; therefore, patients should be assessed for appropriate immunizations against herpes zoster, influenza and pneumococcus before commencing therapy.

Clinical pearls: apremilast

- Apremilast has a favorable safety profile and is likely a viable therapeutic option for elderly patients with psoriatic arthritis.
- Evaluate risks of depression and monitor weight during therapy.
- Routine laboratory monitoring is not required during apremilast therapy.

Key points

- Older patients with rheumatic disorders are at increased risk for therapeutic misadventure due to age-related pharmacokinetic and pharmacodynamic changes, polypharmacy, comorbidities, impaired health literacy secondary to decreased cognition, and provider age bias.
- Rheumatologists along with other members of the allied health care team, can most effectively minimize the risk for medication-related adverse reactions in older patients.
- Familiarity with dosing, monitoring, adverse reactions, medication interactions, and amelioration strategies can improve the safety of disease-modifying antirheumatic drugs in the older rheumatology patient.

Table 1Clinically Relevant Medication Interactions with Tofacitinib. Data from refs^{109–112}

CYP subset	Inhibitors	Inducers
CYP3A4	Clarithromycin, Erythromycin Ketoconazole Itraconazole Diltiazem Verapamil Nelfinavir Ritonavir	Rifampin Phenytoin Carbamazepine
CYP2C19	Fluoxetine Fluvoxamine Isoniazid Ritonavir	Rifampicin Phenytoin Carbamazepine