J R Coll Physicians Edinb 2021; 51: 237–45 | doi: 10.4997/JRCPE.2021.306 **REVIEW**

Safety of long-term use of four common conventional disease modifying anti-rheumatic drugs in rheumatoid arthritis

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Abstract

Conventional disease-modifying antirheumatic drugs (DMARDs) have been used in the management of rheumatoid arthritis for a long time. Whereas methotrexate (MTX) is the anchor drug, leflunomide, hydroxychloroquine and sulfasalazine are used along with MTX either in combination or sequentially. Together these four drugs are the most commonly used DMARDs. They are also used in combination with biological DMARDs (bDMARDs) to enhance their efficacy and MTX in particular to reduce antibodies against anti-tumour necrosis factor. Despite their widespread use, concerns regarding their safety especially when used long-term hinder their optimum use in clinical medicine. In this narrative review we have critically appraised the available literature regarding the safety of these four DMARDs when used long-term.

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Introduction

Timely initiation of therapy is critical to prevent the joint destruction and subsequent loss of function in patients with rheumatoid arthritis (RA). In RA, whereas methotrexate (MTX) is the anchor drug, leflunomide, hydroxychloroquine and sulfasalazine are used along with it, either in combination or sequentially. Together these fours drugs are the most commonly used conventional synthetic disease-modifying antirheumatic drugs (csDMARDs). With ever better understanding of the pathophysiology of RA, several new options beyond csDMARDs such as biological (bDMARDs) and targeted synthetic (tsDMARDs) have emerged.[1] Though the threshold to commence these newer options are decreasing in the current era, it is worth bearing in mind that csDMARDs still form the first-line therapy not only in RA but often also in other autoimmune diseases such as psoriatic arthritis (PsA) and lupus. Because of the chronicity of these disorders, they are often prescribed on a long-term basis, and generally appear to have good retention rates even in the elderly, however, concerns regarding their toxicity when used long term is important vis-à-vis maintenance of efficacy.[2] In this narrative review we have critically appraised the relevant literature regarding the safety of these four DMARDs when used long-term.

Search strategy

Our literature search covered the Medline, Embase, Scopus, Web of Science and Google Scholar databases and included articles published in English between January 1980 and June 2021, but we did not intend to ignore any high-quality relevant earlier literature. The following MeSH terms/keywords were used: methotrexate, hydroxychloroquine, chloroquine, sulfasalazine, leflunomide, anti-rheumatic agents, disease modifying anti-rheumatic drugs, arthritis, rheumatoid, inflammatory arthritis, drug-related side effects, adverse reactions, rheumatoid arthritis, long term, safety, toxicity. Similar to a multinational 3E (evidence, expertise, exchange) initiative which developed recommendations for the management of rheumatic diseases, for the purpose of this review we also defined long-term DMARDs used as two years or longer and appraised the literature accordingly.[3] We have followed the guidelines for writing narrative reviews.[4]

Methotrexate

For RA, the most commonly prescribed DMARD is MTX, which became part of standard treatment in the 1980s (though its usage dates as far back as the 1950s) and is the longest prescribed DMARD by far. Its efficacy, ease of administration,

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dose flexibility, good tolerability, ability to combine with other agents and low adverse effects to efficacy ratio make it the anchor drug for RA and therefore all guidelines endorse MTX in treatment-naïve patients with RA as monotherapy or in combination with other DMARDs.[5,6] Overall, the safety profile of MTX appears favourable, with benefits clearly outweighing the risks. In addition, it has shown mortality benefits in RA.[7] In contrast to its usage in oncology, in rheumatology it is used in a low dose (up to 25-30 mg weekly, orally or subcutaneously) and works more as an anti-inflammatory than as an antimetabolite. The safety profile of MTX was well exemplified in a 13-year-long study of 248 patients with approximately 1,007 patient-years of experience, where it was observed that MTX had a very high five-year continuation rate of 79% (95% confidence interval, 72% to 84%) with very few significant laboratory abnormalities (2.9 per 100 person years).[8] Of the 46 patients (19% of total 248) who withdrew from MTX, 26 did so because of adverse events (oral ulcers and gastrointestinal being most common) and 15 due to lack of efficacy. Some of the adverse events such as acute kidney injury are very rare. Its key toxicities are discussed in detail below.

Hepatic

One of the major concerns of long-term MTX usage is hepatotoxicity. Different studies have shown the variable extent of this toxicity ranging from mild transaminitis on one to cirrhosis at the extreme end. Mild reversible transaminitis has been reported in various studies ranging between 45-55% but in most of them it was not of much concern. Certain factors that were associated with increased risk included advanced age, diabetes, folic acid deficiency, preexisting liver disease, obesity and heavy alcohol consumption. One study retrospectively reviewed the records of 182 patients with RA over 14 years. Out of a total 2,791 liver function tests (LFTs) performed on them, only 94 (3.4%) were found to be abnormal;[9] 2,007 LFTs on 152 patients remained normal, compared with 30 patients who had at least one abnormal result in 784 tests. Twenty-two of these 30 patients with at least one LFT abnormality continued treatment despite the elevation, without further evaluation or change in therapy, and subsequent LFT assessments were within normal limits. More than 70% of patients continued MTX treatment over a mean duration of 38 months with a mean dose of 13 mg.[9] These data further strengthen the long-term safety of the drug by showing that MTX-related liver function abnormality was a rare reason for discontinuation of this drug. Another study involving 254 patients with RA on long-term MTX (average 21 ± 24 months, 452 patient years) indicated that most of the liver enzyme abnormalities occurred within the first four months of therapy.[10] These elevations were fully reversible and did not lead to significant changes in therapy. None of the patients required a liver biopsy. This study underscored the need for laboratory tests to be done in weeks two and four, then monthly for the first four months of therapy, then two to four times per year. In the validation cohort of this study with 135 patients on 298 patient years of MTX therapy, such a strategy was found to be capable of detecting 98.3% of laboratory abnormalities in a timely manner. In a pooled analysis of 27 prospective studies evaluating 3,808 RA patients treated with MTX for a mean duration of 56 months, the prevalence of more than twice the upper limit elevation in liver enzymes was found to be 13%, with permanent discontinuation in only 3.7% of patients.[11]

Methotrexate has been used in combination with other DMARDs for the long-term and even in combination therapy, the drug showed long-term safety except in cases of leflunomide combinations where significantly more liver toxicity was found.[10,12] A recent meta-analysis included 32 double-blind randomised controlled trials ranging from 24 to 104 weeks (mean duration of 47 weeks) involving 13,177 patients with RA, psoriasis, psoriatic arthritis, or inflammatory bowel disease. Of these, 6,877 were on MTX and 6,300 on a comparator.[13] Though hepatic adverse events were common in both groups (cumulative incidence of 11.2% in MTX group vs. 6.3% in the comparator group), MTX was not found to be associated with any increased risk of serious liver outcomes defined as liver failure, hepatic fibrosis, cirrhosis or death due to liver disease.[13]

Only very few studies had a liver biopsy performed on patients with RA taking MTX. In the two studies with baseline biopsies that were available for comparison, there was no evidence of severe fibrosis or cirrhosis after four years of treatment (cumulative dose of MTX around 2,000 mg).[14,15] A case control study analysed the results of liver biopsy in 41 patients (25 with RA) with deranged LFTs.[16] Compared with controls, these patients had shorter (approximately 33 months) of MTX therapy. MTX-specific liver lesions were only seen in 2/41 biopsies. A majority had autoimmune hepatitis-like (AIH-like) lesions (n=17) and nonalcoholic steatohepatitis-like lesions (n=13), suggesting alternative causes of deranged LFTs are more prevalent.[16] A study assessed hepatic fibrosis by measuring the hepatic stiffness by a transient elastography (TE) method (by FibroScan) in 160 patients with RA who had been on MTX for >five years (median duration and cumulative dose of MTX use 317.5 weeks 4,225 mg, respectively).[17] It found that severe hepatic fibrosis or cirrhosis as detected by the TE using FibroScan was uncommon with high cumulative dose of MTX when administered in the low-dose weekly schedule. In addition, the cumulative dose of MTX did not correlate with hepatic fibrosis as assessed by FibroScan.

Pulmonary

Methotrexate is associated with a well-described range of pulmonary effects, from mild cough and pleuritic discomfort to frank pneumonitis. But overall, this risk appears to be small. Prospective studies have not reported any new development and deterioration of the lung function whilst on low-dose MTX. In one such study, 32 patients with RA received low-dose weekly MTX (mean 17 mg) for an average period of 4.4 years; and in the other, 96 patients with RA received a mean weekly dose of 13 mg for a mean duration of 2.9 years.[18,19]

MTX-associated pneumonitis is thought to be a hypersensitivity reaction. To define a MTX-induced pneumonitis, a subacute presentation of dry cough, fever, increasing breathlessness, new onset chest infiltrates, leukocytosis with negative blood

and sputum culture is required.[20] Studies done prior to 2001 have reported higher rates of this adverse event.[21,22] However a meta-analysis of 22 double-blind, randomised, controlled trials (duration ranging from 24 weeks to 104 weeks) analysed a total of 8,584 patients with RA, 4,544 of whom received MTX and 4,040 of whom received placebo or comparator treatments, and concluded that MTX was associated with an increased risk of total infectious adverse respiratory events (RR 1.11, 95% CI 1.02–1.21, I^2= 0%) but was not associated with an increased risk of total non-infectious respiratory adverse events (RR 1.02,95% CI 0.65–1.60, I^2 = 42%).[23] The risk factors of lung disease in RA patients on MTX include older age, diabetes, insulin, hypoalbuminemia and usage of other conventional synthetic DMARDs.[24] The Cardiovascular Inflammation Reduction Trial (CIRT) evaluated the use of MTX (at median dose 16 mg/week for a median duration of 23 months) for cardiovascular risk reduction in 4,786 subjects with a previous history of myocardial infarction or coronary artery disease.[25] Only six (0.3%) cases of possible pneumonitis occurred in the MTX group and one (0.04%) in the placebo. Aforementioned evidence underscores the need for careful surveillance of patients on MTX with a chest X-ray before starting this drug and clinically in high-risk groups to intervene to discontinue the drug prior to the evolution of a more severe clinical picture.[26]

A major concern of long-term MTX therapy in RA is the development of interstitial lung disease (ILD). In this regard, several recent robust studies have been reassuring. In a nested case control study performed within the Brigham Rheumatoid Arthritis Sequential Study (BRASS), a prospective registry of patients with RA, of the 1,100 RA cases, 84 cases of confirmed RA-ILD and 233 matched RA non-ILD controls were compared with the objective of finding out the predictors of ILD in RA. Past or current MTX use was associated with decreased risk of RA-ILD. Further, this study showed that moderate and high disease activity remained statistically significant predictors of RA-ILD (OR 2.22, 95% CI 1.04–4.72 and OR 5.09, 95% CI 1.58–16.4), respectively, compared to remission (*p* for trend 0.003).[27] A study based on the Danish National Patient Register (NPR) and the clinical DANBIO registry analysed 30,512 patients. There was no association between MTX (one or more purchases) and ILD after one or five years of follow up [HR 1.03 (95% CI 0.71, 1.48) and 1.00 (0.78, 1.27), respectively]. In addition, one or more purchases of MTX was associated with a significantly lower risk of respiratory failure after both one and five years [HR 0.48 (95% CI 0.32, 0.73) and 0.54 (0.43, 0.67), respectively].[28] In another study, 78 patients with RA-ILD were evaluated at baseline with high-resolution computed tomography (HRCT) and lung function tests and followed up. In 52 patients who had treatment with MTX, it was associated with survival (HR 0.13, 95% CI 0.02–0.64) even after adjusting for all possible confounding factors.[29] Also, 26 patients not treated with MTX had more severe lung disease, as evidenced with a tendency to have more ground glass extent in HRCT, lower values in percent of predictive value of DLCO and more patients unable to perform pulmonary function tests underscoring the protective effect of MTX on RA-ILD.

Lymphoma and other malignancies

The incidence of lymphoproliferative disorders (LPD) in RA is slightly high; however, the evidence of MTX as a cause for this is limited.[30] Few studies from Japan have reported a high risk of LPD in patients treated with MTX in RA, and a few also observed that there was a spontaneous regression of these LPD once it was stopped.[31,32] Epstein Barr virus reactivation due to MTX was postulated to be responsible for this observation.[32,33] Overall, as the clinical and pathological characteristics of RA-LPD and MTX-induced LPD are the same, it is difficult to implicate MTX as a causative factor of LPD in RA.[34] In a systematic review of literature involving 26 studies, though most studies confirmed an approximate two-fold increase in lymphoma incidence in patients with RA, there was no statistically significant increased risk of lymphoma with MTX.[35]

Cytopenias

Cytopenias caused by MTX are rare but potentially serious complications, which could be idiosyncratic or dose-related.[36] The overall prevalence of hematological toxicity including leucopenia, megaloblastosis, thrombocytopenia and pancytopenia is estimated to be around 3%.[37] Though old age, deranged renal function, low albumin, concomitant drugs and folic acid deficiency are known risk factors, dosing errors have been one of the major contributors to this toxicity and underscores the need for careful prescribing of this drug.[38] Fortunately, these patients usually improve within two weeks of discontinuation of the drug but some may require treatment with folinic acid or colony stimulating factors. A case series of 46 patients with pancytopenia while on MTX found the WBC count on admission to be an important prognostic factor for survival.[39]

Surgery

The safety of MTX in those undergoing surgery is well established. It has been found that patients who continued the drug prior to the surgery faced lesser infections and post-operative complications one year after the surgery.[40] It is advisable not to discontinue MTX before elective orthopaedic surgeries in patients with RA where the disease is well controlled prior to surgery. Similarly, MTX has not been associated with increased risk of intercurrent infections. Analysis of a large retrospective cohort of 27,710 individuals with RA who had 162,710 person years of follow up concluded that MTX did not increase the risk of mild or serious infections.[41] RA flares are reduced when MTX is continued during orthopaedic surgeries.

Gastrointestinal

One of the major reasons for discontinuation of MTX is the gastrointestinal adverse effects in the form of mucositis, and nausea (sometimes anticipatory) and vomiting. Though these adverse effects are mild, patients are often reluctant to continue the therapy. In such cases, dose reduction, folic acid supplementation or ingestion of coffee with MTX may ameliorate the problems.[42] The other alternative is to switch the patients to subcutaneous MTX which is found to improve the compliance as well as the response to therapy and thus can avoid unnecessary biologicals.[43]

Pregnancy and lactation

Methotrexate is a category X drug during pregnancy due to its ability to cause miscarriage and congenital malformations related to heart, CNS and the skeletal system.[44] Therefore women at childbearing age have to be counselled and appropriate contraception advised whenever MTX is prescribed. However, inadvertent exposure and accidental pregnancy whilst on MTX therapy either pre-conception or during the first trimester might happen. A multicentre cohort study analysed 324 MTX-exposed pregnancies (188 exposed post-conception, 136 exposed pre-conception), 459 disease-matched comparison women, and 1,107 comparison women without autoimmune diseases. Post-conception administration of MTX at less than 30 mg/week was associated with an increased risk of major birth defects and spontaneous abortion, however there was no such increase in women exposed to MTX pre-conception.[45] Similarly, there was no increased risk of adverse pregnancy outcomes after paternal low-dose MTX was reported.[46] Methotrexate is contraindicated in lactation, since it is secreted in breast milk and can accumulate in neonates.[47]

Hydroxychloroquine

Hydroxychloroquine (HCQ) has a variety of immunomodulatory and anti-inflammatory effects. In addition, it also protects against thrombosis and provides additional metabolic benefits by controlling hyperglycemia and hyperlipidemia, thus claiming a very important position in the treatment of autoimmune diseases with cardiovascular risks.[48] It is used in the management of lupus and RA, where the drug may be continued even for a lifetime, especially in the former.[49]

The short-term adverse effects are usually gastrointestinal (nausea and diarrhea) and dermatologic (rash and pigmentation), which usually require symptomatic treatment or may lead to discontinuation if not tolerated. Cases of HCQ/Chloroquine (CQ) induced myopathy have also been reported where discontinuing HCQ/CQ and symptomatic treatment are the mainstay.[50] The gastrointestinal adverse effects are usually not seen over the long term, which improves the overall compliance of this drug. Rarely, HCQ can lead to anemia especially in individuals known to suffer from G6PD deficiency. However, a recent study showed no such risk of hemolytic anemia in G6PD deficient patients with more than 700 months of HCQ exposure.[51] Similarly, in another retrospective study of 18 G6PD deficient patients exposed to HCQ for more than 500 months, no evidence of hemolysis was found.[52]

Few case reports of cardiac conduction disorders and cardiomyopathy have been reported with the use of HCQ, particularly in combination with other medications.[53] Although rare, it can be potentially serious. At present, there is no consensus as to the best methods and interval to monitor cardiotoxicity of long-term HCQ therapy.[54] A recent systematic review of 127 patients with cardiotoxicity with long-term use of HCQ or chloroquine reported conduction disorders as the main cardiac adverse effect (85% of patients) but was unable to quantify the risk due to the absence of any randomised controlled trials.[55] Nevertheless, it has been suggested that HCQ withdrawal should be considered even when asymptomatic conduction defects are present to avoid irreversible damage.

On the whole, development of retinopathy is a risk of long-term HCQ therapy, which is certain but unpredictable. Moreover, the condition is untreatable, and the retinopathy tends to be progressive even after cessation of the drug.[56] Chloroquine is more toxic and leads more frequently to retinopathy; hence it is rarely used in practice currently. If used, the safe dose is 2.3 mg/kg of body weight per day, beyond which it is toxic.[57] The prevalence of HCQ-induced retinopathy has been estimated to be around 7.5% with the use of newer screening and diagnostic techniques like spectral-domain optimal coherence tomography (SD-OCT).[58] The earlier reports of lower risk (<2%) were based mainly on the low sensitivity of the available diagnostic techniques and use of poorly defined criteria for retinopathy. Racial differences in the pattern of toxicity have also been reported, with Asians showing more peripheral defects and extra-macular defects.[59] The risk of retinal toxicity correlates with higher daily doses, duration of use, concurrent tamoxifen therapy, kidney disease, and lower weight. Age and gender have no significant association with toxicity. A drop in renal function by approximately 50% leads to a doubling of the risk of retinopathy. The daily dose recommendation has recently been changed from 6.5 mg/kg lean body weight to 5 mg/kg real body weight for patients without additional risk factors with a maximum of 400 mg during the first five years of treatment. At the dose of 5 mg/kg of real body weight, the risk of toxicity is <1% in five years, less than 2% up to the initial 10 years and rises up sharply to 20% past 20 years of usage.[60]

The UK Royal College of Ophthalmologists (RCO) and American Academy of Ophthalmology (AAO) both advise that the initial dose for HCQ should not be more than 5 mg/kg of real body weight, and this dose should be reduced for renal insufficiency and old age. Both guidelines had recommended baseline testing should ideally be done within six months of starting therapy and at a maximum by at least a year.[57,60] Visual field defects in supero-nasal part in visual field testing and thinning of the photoreceptor layer in SD-OCT are considered definitive signs of HCQ toxicity. The 2021 version of RCO guidelines suggested usage of SD-OCT and wide field fundus auto fluorescence (FAF) as a screening test since the Humphrey 10-2 field testing was highly time consuming.[61] Importantly, these latest 2021 RCO guidelines have done away with baseline screening before initiating on HCQ based on a large cohort study.[62] Once HCQ toxicity occurs it is not reversible, so the current RCO guidelines advocate the 5 x 5 rule: the dose is to be maintained <5 mg/kg body weight and screening is to start from >5 years of usage.[61] Annual examination is thereafter recommended for patients with high risk such as renal disease, tamoxifen use, and daily dose of more than 5 mg/kg and preexisting macular disease. In low-risk patients, annual exams are recommended only after five years of continuous HCQ usage.

Table 1 Recommended laboratory monitoring for DMARDS in RA

Drug name	Liver function test	Complete blood count	Serum creatinine	Reference
Methotrexate	Every 1-2 months	Every month	NA	PI[87]
	ALT/AST at baseline, every 2-4 weeks for 3 months, every 8-12 weeks next 3 months, every 12 weeks thereafter	At baseline, every 2-4 weeks for 3 months, every 8-12 weeks next 3 months, every 12 weeks thereafter	At baseline, every 2-4 weeks for 3 months, every 8-12 weeks next 3-6 months, every 12 weeks thereafter	ACR[88]
	ALT/AST every 2 weeks for 6 weeks till dose stable, then monthly for 3 months and then at least once in 12 weeks	CBC every 2 weeks till dose stable, then monthly for 3 months and then at least once in 12 weeks	Calculated GFR or creatinine every 2 weeks till dose stable, then monthly for 3 months, then at least in 12 weeks	BSR[89]
Leflunomide	ALT monthly for 6 months, thereafter every 6-8 weeks.	CBC at baseline, monthly for 6 months, thereafter every 6-8 weeks	NA	PI[90]
	ALT/AST at baseline, every 2-4 weeks for 3 months, every 8-12 weeks for 3-6 months, every 12 weeks thereafter	CBC at baseline, every 2-4 weeks for 3 months, every 8-12 weeks for 3-6 months, every 12 weeks thereafter	At baseline, then every 2-4 weeks for 3 months, then every 8-12 weeks for 3-6 months, then every 12weeks thereafter	ACR[88]
	ALT/AST every 2 weeks until stable dose for 6 weeks, monthly for 3 months, thereafter every 12 weeks	CBC every 2 weeks until dose stable for 6 weeks, monthly for 3 months, thereafter every 12 weeks	Calculated GFR or creatinine every 2 weeks until dose stable, monthly for 3 months, thereafter every 12 weeks	BSR[89]
Hydroxychloroquine	ALT and AST at baseline, none thereafter	CBC at baseline and none thereafter	At baseline	ACR[88]
Sulfasalazine	ALT, AST at baseline, every 2-weeks first 3 months, every 8-12 weeks next 3-6 months, every 12 weeks thereafter	CBC at baseline, every 2-4 weeks for 3 months, every 8-12 weeks next 3-6 months, every 12 weeks thereafter	At baseline, every 2-4 weeks for 3 months, then every 8-12 weeks next 3-6 months, every 12 weeks thereafter	ACR[88]
	ALT/AST every 2 weeks until stable dose for 6 weeks, monthly for 3 months, every 12 weeks thereafter	CBC every 2 weeks until stable dose for 6 weeks, monthly for 3 months, every 12 weeks thereafter	Calculated GFR or creatinine every 2 weeks until stable dose for 6 weeks, monthly for 3 months, every 12 weeks thereafter	BSR[89]

Hydroxychloroquine has been considered safe in pregnancy and though it gets secreted in breast milk, no retinal changes or cutaneous changes are observed in neonates.[63]

Leflunomide

Leflunomide is an oral pyrimidine synthesis inhibitor. The long-term efficacy of this drug in RA has been well documented.[64] Various clinical trials have also shown its efficacy and good tolerability when combined with other DMARDs.

In clinical trials on patients with RA, the most frequent side effects of leflunomide compared with placebo were diarrhoea (27 versus 12%), elevated liver enzymes (10 versus 2%), alopecia (9 versus 1%), and rash (12 versus 7%).[65] Most adverse events are usually mild and transient, and they tend to resolve with continued leflunomide treatment, although in some cases it may be useful and necessary to reduce the dose of leflunomide. In another study, mild to moderate adverse effects were seen in 19% patients, most of which resolved spontaneously and did not account for discontinuation of the drug.[66] Even in patients with psoriatic

arthritis, leflunomide is well tolerated and the discontinuation rate has been found to be around 13%.[67] Furthermore, in RA, the safety profile appears to improve with long-term use.[68]

The most important concern for long-term leflunomide therapy is hepatotoxicity. However, most of the observational studies have shown that liver enzyme elevations usually occur during the first six months of therapy and resolve during continued follow up.[69] Similarly, clinical studies have shown the hepatic event rate to be lower than with other DMARDs or biological agents.[70] In its review in 2003, the FDA found that 2-4% of leflunomide-treated patients experienced mild elevations in liver enzymes but serious hepatotoxicity events were rare.[71] It is advisable to do a baseline liver function test prior to starting the treatment and then monthly for the first six months and thereafter every 8-12 weeks (Table 1). In cases where leflunomide is prescribed with MTX, monitoring must be done monthly.

New onset hypertension has been reported at an incidence of ~1–2% with leflunomide treatment, and usually occurs during the first three months of therapy.[72] Clinically significant hypertension as an adverse event, however, was not found on long-term therapy.[73] Management options include dose reduction and treatment with antihypertensive agents, as appropriate. Leflunomide has also been associated with modest weight loss, unrelated to disease activity or treatment failure.[74] However, this weight loss has not been significantly associated with discontinuation of the drug or an increase in mortality risk.

Another important concern with leflunomide is pulmonary toxicity. Initial observational studies from Japan and USA with leflunomide reported an increase in the risk of interstitial lung disease (ILD).[74-76] Similarly, two other systematic literature reviews of observational studies and case reports also showed an association of leflunomide with a rapidly developing potentially lethal ILD most commonly in the first three months of initiation.[77,78] Cavitary pneumonia is another rare lung disease reported with leflunomide as isolated case reports.[78,79] However, a recent meta-analysis of eight randomised controlled trials found no evidence of increased pulmonary adverse events with leflunomide therapy for RA.[80]

Leflunomide is considered embryotoxic and teratogenic based on animal studies. Pregnancy must be excluded prior to therapy and counselling for contraception must be done for all women of childbearing age. In case of accidental pregnancy, the drug must be stopped immediately, and an 11-day course of cholestyramine (8 gm three times a day) is recommended to bring down the drug level to <0.02 mg/L. The same regimen is to be followed for both men and women desiring to conceive. In a small survey of women on leflunomide who conceived, even though none developed congenital malformations, it is advisable to avoid pregnancy.[81]

Sulfasalazine

Because of a relatively lesser efficacy amongst all DMARDs, sulfasalazine (SSZ) is usually prescribed as a part of combination therapy for RA. Most of the studies have shown a good efficacy of this drug when combined with MXT. The toxicities are low and almost all of them occur during the initial phase of therapy, so long-term use of SSZ is safe.

The most common adverse effects accounting for more than 25% of withdrawal are gastrointestinal and cutaneous side effects.[82] Anorexia, headache, vomiting, diarrhea and gastric distress are common in the early therapy or during dose escalations. Pruritic rash occurs in 5% patients especially in those with a history of sulpha allergy.[83] Very rarely it may cause a syndrome of drug reaction with eosinophilia and systemic symptoms (DRESS).[84] Serious agranulocytosis has been reported but mostly observed in the first six weeks of treatment. A new onset fever with or without sore throat after starting this drug must be seen with suspicion of agranulocytosis. Routine laboratory investigations are recommended once monthly in the initial three months and thereafter once every three months during long-term treatment (Table 1). Other infrequent adverse effects reported are hepatotoxicity, eosinophilic pneumonia, anaphylactic reactions and megaloblastic anemia.[85,86]

Temporary oligospermia has been reported in males, therefore stopping it in males three months prior to conception should be considered. It is considered safe both in pregnancy and lactation and is a commonly continued DMARD in RA with pregnancy.

Conclusion

On the whole, the four conventional DMARDs reviewed herein are generally safe to be used long-term in the management of RA. With a focus on diagnosing RA early and initiating the DMARDS at the earliest, it is likely that they would be prescribed more frequently in future. It is therefore critical to be aware of the adverse effects and safety concerns of these drugs so as to provide the necessary information to the other caregivers as well as to the patients. Since the therapy is prolonged, it is mandatory to follow the good clinical practice of recommended laboratory monitoring (Table 1) for these drugs and to guide the therapy to achieve the desired outcome for RA.[87-90] Such close monitoring is not only a crucial part of patient care, but it is also a way to attenuate the adverse effects and optimise the therapy. Effects of drugs on pregnancy and lactation need to be addressed to avoid accidental pregnancies and may save one from having to make difficult decisions later. The expansion of knowledge of precision medicine in rheumatic diseases may further help us in individualising the therapy, thereby reducing their adverse effects when used long-term.

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