Long-term safety of methotrexate in the treatment of rheumatoid arthritis

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ABSTRACT
Methotrexate (MTX) has been the anchor treatment in rheumatoid arthritis (RA) over the last 15 years, and is used in combination with biologic agents to enhance efficacy over the last decade or so. The safety profile of MTX has been studied over 25 years with very few clinically important adverse events in the weekly low-doses used for RA treatment. The importance of MTX in earlier and more aggressive management of RA patients cannot be overstated. MTX courses show some of the longest continuation rates reported in clinical medicine, due to both effectiveness and safety. The safety profile of MTX indicates that it is among the safest of any medication used for the treatment of any arthritis. Better information on the effectiveness and safety of weekly-low dose MTX should be communicated to all health professionals involved in the management of RA patients.

Introduction
Methotrexate (MTX) has been one of the most studied disease modifying antirheumatic drugs (DMARD), for efficacy, effectiveness, and safety, in both short-term randomised clinical trials (RCT) and long-term clinical observational studies.

MTX monitoring guidelines
Initially, MTX was reserved for patients who had long disease duration and had tried and failed multiple other medications. With recognition that early and aggressive treatment with MTX had led to improved outcomes, MTX use expanded to earlier use in the course of RA. Guidelines were developed for the monitoring of adverse events with MTX, particularly liver function abnormalities.

The 1994 American College of Rheumatology (ACR) guidelines (1) recommended laboratory monitoring every 4–8 weeks, based primarily on data from patients who had participated in clinical trials. In patients with sustained elevation of liver function tests, a liver biopsy was recommended, in part echoing the common practice of liver biopsies in psoriasis and psoriatic arthritis patients using MTX. However, the safety profile of MTX in patients with psoriasis and psoriatic arthritis historically has differed from the safety profile in patients with RA. Subsequent monitoring guidelines for other DMARDs have been for the most part derived from MTX monitoring guidelines.

A review of the 1994 MTX monitoring guidelines (2) suggested that the patients analysed to derive the recommendations may differ considerably from contemporary patients in whom MTX is widely accepted as the standard first line treatment for RA. Most patients have shorter disease duration when MTX is initiated at this time compared to previous decades. In addition, there are possibly some methodological problems with the way data were collected on patients included in the ACR guidelines, where about a third of the patients were counted more than once, as they were reported, and counted multiple times for each time a manuscript from the same cohort was published. This may make the results less applicable to everyday– and especially current-MTX using RA patients.

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indicated that liver enzyme abnormalities in patients taking methotrexate virtually always occurred within the first 4 months of therapy (6). These elevations did not lead to changes in therapy, and liver biopsy was not performed in any of the patients. The vast majority of laboratory abnormalities were fully reversible, and no costly complications were seen.

The data led to a suggestion that monitoring should be more frequent (every 2–4 weeks) over the first 4 months and then performed every 4–6 months, which was validated in another cohort of RA patients from another hospital in Vienna. It was calculated that a mean of 48–78% of costs could be saved by implementing the proposal for less frequent monitoring (7).

In another study, 248 RA patients who had been treated with MTX over 13 years in Nashville, TN were reviewed (8). In this cohort with over 1000 patient-years of follow-up, the probability of continuing MTX at 5 years was 79%. Severe laboratory abnormalities occurred in 2.9/100 patient-years, and for AST over 80U/l this was 0.9, 1.1 for albumin <30g/l, 0.7 for white blood cell (WBC) count <3.0 and 0.3 for platelet counts <100x10^3/l. None of these laboratory abnormalities progressed to clinical disease or further worsening, and no liver biopsies were performed. Permanent discontinuations of MTX occurred in 46 (19%) of patients, about one-half due to adverse events and a third due to inefficacy. Only two patients stopped their MTX due to laboratory abnormalities, both of which were low WBC values, likely due to other causes. These patients were told by their rheumatologist that up to two drinks a day was possible, and that they need not to abstain from alcohol. MTX continuation rates were considerably higher than reported for TNF inhibitors in clinical care, in which continuation rates at 2 years for anti-TNF agents were about 50% (9) and 60% (10). In conclusion MTX was very well tolerated with minimal clinically significant adverse events and was suggested to be possibly among the safest treatments for rheumatoid arthritis.

A systemic literature search of the long-term safety of MTX monotherapy in RA included 88 studies of MTX over 12 years of treatment (11). Discontinuation rates for MTX due to toxicity were less than that reported for sulfasalazine, gold and penicillamine. Long-term use did not appear to be a risk factor for serious infections, and also provided a survival benefit by reducing cardiovascular risk. The prevalence of elevated liver enzymes (more than twice the upper limit of normal) was seen in 13% of patients, but only 3.7% stopped MTX due to these abnormalities. The data suggested little risk for developing liver fibrosis or cirrhosis. There were insufficient data to make a firm conclusion about risk of lymphoma and other malignancies, although there was no strong evidence of increased risk.

Another systematic review and meta-analysis examining MTX monotherapy versus MTX combination therapy with non-biologic DMARDs in RA showed similar results (12). Nineteen trials with 2025 patients were studied. MTX alone showed no increased toxicity risk when compared to MTX and DMARD combinations, except in the case of leflunomide combination, in which more liver and gastrointestinal toxicity was noted. RCT of biologic agents since the mid 1990s have also added to our knowledge about MTX use as is discussed elsewhere in this supplement. Most of these are short-term trials lasting fewer than 12 months, with open label extensions of the biologic agents continuing up to 5 years. In the short-term results of these trials there are no new safety signals in MTX-treated patients, as would be expected in a selected group of patients who do not have any other chronic diseases and are limited in the other medications they can take during the trial.

It has been suggested that this safety and efficacy profile can facilitate the use of MTX as an n-of-1 trial (13). Patients suspected of having RA may be started on low dose prednisone and MTX, for a trial period of 3–6 months, in place of anti-CCP, MRI or ultrasound testing. The rationale for this n-of-1 trial is based on evidence about the safety and efficacy of MTX, which equals a biologic agent when used alone; a combination of a biologic agent and MTX...
has greater efficacy than either does alone. By starting this therapy early, a patient can be identified as a MTX responder or non-responder, with a need for more aggressive therapy at the earliest time in disease course. If a patient is responding at the end of the trial period, he/she can continue the treatment or a trial of stopping MTX can be tried. If the patient flares, he/she can reinstate MTX and no time has been wasted and the patient has been taking MTX since first day. If there is inadequate response, then there is good reason to add a biologic agent.

The new RA diagnostic criteria are more and more based on “likelihood” of having RA, rather than on a definitive statement, which may mean there is no need to wait for a definite diagnosis of RA before starting a disease modifying treatment. This may lead to the treatment of some patients with fibromyalgia and self-limited post infectious arthritis with MTX for a limited time, but given the safety record of MTX this would lead to very few clinically significant problems.

Conclusion

As methotrexate prescribing patterns have changed from initially being reserved for patients who had “climbed the RA treatment pyramid” to earlier in the disease course, the toxicity profile has improved. Patients are relatively healthier early in their disease and appear to be less vulnerable to adverse events (14). In multiple cohorts, methotrexate appears to have very few clinically significant side effects, possibly due in part to the routine use of folic acid supplementation. Both rheumatologists and primary care physicians should explain to patients and other doctors involved in the patient’s care the safety of weekly, low dose MTX, and expand the use of this beneficial treatment as early as possible in RA management.

References