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CURRENT OPINION

Optimizing Methotrexate Treatment in Rheumatoid Arthritis: The Case for Subcutaneous Methotrexate Prior to Biologics

Poonam Sharma[1] · **David G. I. Scott**[2]

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Abstract Methotrexate is the most common disease-modifying antirheumatic drug (DMARD) used in the treatment of rheumatoid arthritis (RA). Current evidence supports its efficacy in the treatment of RA, resulting in improved short-term disease control and long-term outcomes in terms of radiographic progression. Oral methotrexate has traditionally been used first-line due to various reasons, including ease of administration, low cost and easy availability. A methotrexate dose of >15 mg/week is generally required for disease control but oral methotrexate may be only partially effective or poorly tolerated in some patients. The rationale for using subcutaneous (SC) methotrexate is based on its improved bioavailability at higher doses and better tolerability in some patients who have side effects when receiving oral methotrexate. Current guidance advocates 'treating to target', with the aim of inducing remission in RA patients. In some patients, this can be achieved using methotrexate alone or in combination with other traditional DMARDs. Patients who have not responded to two DMARDs, including methotrexate, are eligible for biological therapy as per current National Institute for Health and Care Excellence (NICE) guidance in the UK. Biological treatments are expensive and using SC methotrexate can improve disease control in RA patients, thus potentially avoiding or delaying the requirement for future biological treatment.

Key Points

Subcutaneous methotrexate should be routinely considered in patients with active rheumatoid arthritis, prior to using biological therapy.

1 Background

Rheumatoid arthritis (RA) is a chronic disabling condition that affects approximately 1 % of the UK population [1]. The treatment of RA has been revolutionised in the past few decades with the advent of disease-modifying antirheumatic drugs (DMARDs) and biologics. 'Treat to target' recommendations advocate remission as a goal for treatment of RA [2]. Methotrexate is described as effective and is the best-studied disease-modifying drug used in the treatment of RA. In a recent trial of methotrexate versus combination DMARDs in early arthritis, methotrexate and steroids were as effective as combination DMARD treatment [3]. This has previously been demonstrated in another trial of 205 RA patients in whom methotrexate monotherapy showed similar efficacy to combination therapy [4]. National Institute for Health and Care Excellence (NICE) guidance on the management of newly diagnosed RA advocates early combination therapy, including methotrexate, with the aim of inducing remission [5].

Methotrexate is an analogue of aminopterin, which was originally used in 1948 to treat leukemia in children.

✉ Poonam Sharma
poonam.sharma@pbh-tr.nhs.uk

[1] Department of Rheumatology, Peterborough and Stamford Hospitals NHS Foundation Trust, Peterborough City Hospital, Bretton Gate, Peterborough PE3 9GZ, UK

[2] Department of Rheumatology, Norfolk and Norwich University Hospitals NHS Foundation Trust, Norwich, UK

Aminopterin was gradually replaced by methotrexate in the 1950s due to its less toxic nature. Since then methotrexate has been widely used in various autoimmune conditions, including RA [6], and in 1986 was licensed by the US FDA for the treatment of RA [7].

2 Mode of Action

Methotrexate is commonly administered orally as a weekly dosage of between 7.5 and 25 mg, but can also be used by other routes of administration, including subcutaneously, intramuscularly and intravenously. Methotrexate is a folate analogue and, because of its hydrophilic nature, it uses a carrier-mediated transport [8]. The exact mechanism of action of methotrexate in RA remains unclear; however, there are various proposed mechanisms of action, one of which revolves around folate antagonism. Methotrexate inhibits dihydrofolate reductase and other folate-dependent enzymes, thus preventing purine and pyrimidine synthesis in the S phase of the cell cycle, which is required for proliferation of actively dividing cells. A study by Genestier et al. demonstrated that methotrexate induces apoptosis and clonal deletion of activated T cells [9]; the other proposed mechanism revolves around adenosine release. Using a rat model, Montesinos et al. demonstrated that adenosine generated endogenously mediates the anti-inflammatory effects of methotrexate [10]. Other modes of action have also been proposed, including inhibition of synthesis of transmethylation products that accumulate in chronically inflamed tissues, and reduction in intracellular glutathione levels, leading to diminished macrophage recruitment and function [11].

Bioavailability of low-dose oral methotrexate is highly variable, ranging from 25 to 100 %, but is usually around 70 % [12]. There is significant individual difference in the absorption of oral methotrexate from the gastrointestinal tract, resulting in variable serum concentration [13]. Methotrexate administered by the intramuscular (IM) route is better absorbed and associated with improved disease control [14, 15], and IM methotrexate is well tolerated and has good efficacy. This has been shown by Rau et al. in comparative trials of RA patients randomised to treatment with IM methotrexate versus gold therapy [16, 17]; however, IM injections cannot be easily self-administered by patients in contrast to subcutaneous (SC) injections. Pharmacokinetic studies have shown similar bioavailability of methotrexate after SC or IM administration [18], making SC methotrexate an attractive option due to its ease of administration. In addition, SC injections are generally less painful than IM injections.

3 Rationale for Subcutaneous Methotrexate

SC methotrexate has been shown to have better tolerability and efficacy compared with oral methotrexate. In a retrospective review of 762 RA patients, one-third of the patients had stopped oral methotrexate due to poor tolerability [19]. This is an important limitation of oral methotrexate. A 6-month trial of 375 RA patients receiving oral versus SC methotrexate showed a statistically significant difference between the two groups. At 24 weeks, 78 % of patients in the SC methotrexate group had achieved an American College of Rheumatology (ACR) 20 response compared with 70 % in the oral methotrexate group ($p < 0.05$) [20]. In another trial, switching to SC methotrexate from an oral formulation due to insufficient response or adverse events resulted in 63 % of patients showing improvement in disease activity [21]. In another study of 70 RA patients treated with SC methotrexate, 53 % remained on SC methotrexate over a mean follow-up period of 1.8 years without needing to be considered for biologics [22].

Recent data from an observational study of the Canadian Early Arthritis Cohort (CATCH) also supports improved efficacy and tolerability of SC methotrexate over oral methotrexate. In this cohort, patients who were initially treated with SC methotrexate had a lower rate of treatment failure and greater reduction in Disease Activity Score (DAS) 28 compared with the group receiving oral methotrexate [23].

A head-to-head comparison of oral versus SC methotrexate in 47 patients with RA demonstrated a linear increase in systemic exposure after SC methotrexate compared with a plateau seen in patients receiving oral methotrexate at doses $\geq$15 mg/week. This would suggest little or no advantage in increasing oral methotrexate beyond 15 mg/week. However, administration of SC methotrexate continues to exhibit a linear, dose-proportional increase with no plateau, therefore dosage increase can be expected to result in increased efficacy [24].

Gastrointestinal side effects are common with oral methotrexate and, in the majority of cases, switching to the SC form has been shown to alleviate this problem in the dermatology setting [25]. Historically, the use of SC methotrexate was limited due to the logistics of dispensing such cytotoxic medications and patients therefore having to attend hospital on a weekly basis for their injections. A recent review of the patterns of methotrexate use in RA patients in the US identified that SC methotrexate is underutilized (possibly associated with this problem) [26]. A prefilled methotrexate pen is now available and is very well tolerated. In a study of 120 patients, 75 % preferred a prefilled pen over syringes [27].

The '3E initiative' also recommends consideration of the use of SC methotrexate in the treatment of RA in patients who cannot tolerate oral preparations or have ongoing active disease [28]. It has been calculated that the use of SC methotrexate following oral methotrexate failure has the potential to save an estimated £7197 per patient in the first year of therapy and £9.3 million per year nationally in new patients with RA [29]. This is a significant saving in the current financial climate. The MENTOR study was a retrospective review of 196 patients who were switched from oral to SC methotrexate. Less than 10 % of these patients required biologic therapy in the following 2 years, which supports the proposition that SC methotrexate is both effective and well tolerated in the treatment of RA. Results from the MENTOR study also indicate high continuation rates, with 83 % of patients still receiving SC methotrexate at 1 year [30].

Various trials have looked at using biologic therapies earlier in RA to induce remission. However, methotrexate monotherapy has been shown to be as equally efficacious as methotrexate and etanercept combined in inducing remission induction in patients with early RA [31], therefore the widespread use of early biologic drug usage needs further study. The threshold for using biologics in the UK is considered high (DAS >5.1) compared with other European and Western countries, many of whom use a lower DAS threshold (e.g. 3.2). The British Society for Rheumatology has suggested using this lower threshold in the UK [32]. We believe that the best way to take this forward would indeed be to lower the threshold, but add to the definition of methotrexate failure as "failure of oral and SC methotrexate" (as also stated in the Canadian biologic guidelines), which would dramatically reduce the potential impact (clinical and financial) of such a change in guidelines [33].

4 Limitations

The evidence for toxicity with parenteral methotrexate is inconsistent across the various clinical trials. Although confirming superiority of SC methotrexate over oral methotrexate, the study by Braun et al. showed that the gastrointestinal adverse events were similar between the two routes of methotrexate administration, with more discontinuations in the SC group [20]; however, other studies have shown better gastrointestinal tolerability of SC methotrexate [22, 25]. In addition, the cost of the SC methotrexate formulation will vary from country to country and remains an important consideration in the current financial climate.

5 Conclusion

Oral methotrexate remains the first drug of choice in the treatment of RA due to the combination of its efficacy, tolerability, availability, and affordability. SC methotrexate should usually be considered prior to biologics in patients with poor tolerance of oral methotrexate or resistant disease.

Compliance with Ethical Standards

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