Parenteral Methotrexate for the Treatment of Rheumatoid Arthritis

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Abstract

Methotrexate (MTX) is the anchor treatment for rheumatoid arthritis (RA) and has been very thoroughly studied in many different patient populations, as monotherapy and in combination with various other disease modifying antirheumatic drugs and biologic agents, as they became available. It has a well-established safety and efficacy profile and is the preferred first line agent for RA treatment. Historically, oral (PO) preparations of MTX have been used in the USA with minimal parenteral (subcutaneous, SC, and intramuscular, IM) administration. Several shortages of drug availability in a parenteral form have been possibly one of the reasons for this low level of use. Several studies have looked at the role of parenteral MTX in RA treatment, and these overall demonstrate better tolerability, bioavailability, and possible efficacy of MTX compared with PO preparation.

Methotrexate (MTX) is the anchor treatment for rheumatoid arthritis (RA) and has been very thoroughly studied in many different patient populations, as monotherapy and in combination with various other disease modifying antirheumatic drugs and biologic agents, as they became available.1 It has a well-established safety and efficacy profile and is the preferred first line agent for RA treatment. Historically, oral (PO) preparations of MTX have been used in the USA with some subcutaneous (SC) and other parenteral administration. Several shortages of drug availability in a SC form have been possibly one of the reasons for this.

A large majority of trials have been done with PO MTX, and the use of SC MTX for the treatment of RA is limited. We will review the available and clinically relevant data and try to better define the role and place of SC MTX in the treatment of RA.

One of the potential issues with PO MTX is that as it is a tablet there may be some compliance issues, and these have been reported to be somewhere around 15% of patients not taking PO MTX the way they have been prescribed.2 SC formulation, as more and more patients become comfortable with self-injections, especially with the availability and widespread use of injectable biologics, may be preferred just because of ease of use issues especially if the patients do not have to prepare the dose to inject themselves.

Clinical Trials

One major issue in the treatment of RA is MTX inadequate response, which has been described in many different ways, and a standardized definition does not exist. It is sometimes hard to distinguish which patients are truly not responding enough to a certain dose of MTX or if it is due to bioavailability. One study which looked at this issue3 switched 24 patients (17 females) from oral MTX (mean = 17.5 mg/week) to parenteral MTX (mean = 15 mg/week) and saw that 20 of them improved, where 3 were unchanged, and only one patient got worse.

In another interesting study, patients had to switch from parenteral MTX to oral MTX due to a shortage. Investigators wanted to see if parenteral MTX may be more efficient than oral MTX at the same dose in the same patients with RA. Eight patients were analyzed, all were in stable remission for about 3 years before the switch and relapses occurred rapidly after the switch.4

Another study looked at the caveats of using parenteral MTX in the treatment of rheumatic disease. One hundred and two patients who were on oral MTX were switched to
IM/IV. Forty-four switched due to lack of efficacy, 27 of which received oral dose of 17.5 mg/week or higher. After the switch, 21 felt better on parenteral dose, and 21 felt no change between oral and parenteral. Other reasons for switching were: 29 switched following advent of nausea, 4 switched after developing mucositis, 5 because of non-specific malaise, 4 because of abdominal pain, and some due to weight gain.6

An important issue is cost control in RA treatment. Hassanzadeh and coworkers examined the financial and health benefits of using SC MTX before using anti-TNF-α therapy. Two hundred fifty-six patients tried anti-TNF-α therapy, and 68 had tried SC MTX. Most switched to SC from oral MTX because it was ineffective or not tolerated because of adverse effects. Of these patients, 29% of 68 stopped due to adverse effects, 22% of 68 were also on anti-TNF-α therapy, but interestingly, 49% of 68 were established with stable disease while taking SC MTX only. Investigators also calculated that 1 year of anti-TNF-α therapy for a single patient was £9,295 ($14,904 US), whereas equivalent dosage of SC MTX was £927.68 ($1,487.53 US),6 which brings up the interesting issue of the role of SC MTX as a cost control agent.

A post hoc analysis of the CAMERA study5 looked at the 57 patients who needed to change from PO to SC MTX out of the 151 patients in the study—21 because of adverse events and 36 because of inadequate efficacy. The mean decrease in the DAS28 score 1 month after taking SC MTX was 0.30 points, 0.21 points more than before taking the step. Following the switch to SC MTX, 36 patients responded (had an equal or better course in DAS28 compared to preceding months), and 21 did not. It was noted that change from PO to SC was useful specifically for those in the inadequate efficacy group.

In a randomized double blind clinical trial,8 investigators compared the clinical efficacy and safety of SC versus PO administration of MTX in patients with active RA. They enrolled 384 patients; 194 received SC, and 190 received PO MTX. Most were female (75%, median age = 59), and most patients had early RA. Patients were randomly assigned to receive 15 mg/week of MTX either orally or SC for 24 weeks. After 24 weeks, the percentage of patients with ACR20 and ACR70 response was significantly higher in the group receiving SC MTX than the group receiving oral MTX (85% versus 77% and 62% versus 59%, respectively). At week 24, the number of swollen joints and tender joints was lower in the SC group than in the oral group (2 versus 3 and 3.3 versus 3.7, respectively). Overall, 66% of SC MTX patients reported an adverse event during the study, compared to 62% for oral. When SC MTX was begun at the starting dosage of 15 mg/week, ACR20 response rates as high as 80% were achievable and almost 90% for early but more established RA. Investigators suggested that patients with poor compliance, inadequate effectiveness, or GI side effects of MTX should consider a switch from PO to IM/SC administration. A switch from PO to SC MTX and a switch from a lower dosage to a higher dose of SC MTX were both effective in 30% and 23% of patients, respectively.

Withdrawal of study medication was seen more often in the SC MTX group than in the oral MTX group. Overall, GI adverse effects were similar between the two routes.

A smaller study looked at escalation to parenteral MTX in active RA that has been unresponsive to conventional doses of PO MTX.6 Sixty-four patients were switched from oral MTX to 15 mg/week IM MTX. These were active RA patients with a mean duration of disease was 9 to 10 years with a previous exposure to two to three DMARDs on average. They had also been receiving MTX for a median of 2.5 years at a stable dose of 15 to 20 mg/week for at least 2 months prior to the study. Baseline DAS28 was 5.6, which after 6 weeks of IM MTX, improved by a mean of 0.42 units. At 6 weeks, 54 patients still had a DAS28 of greater than 3.2, and they were divided into two groups based on demographic, disease, and health status characteristics. They had a mean duration for disease of approximately 10 years, with a mean baseline of DAS28 at 5.4. The median dose of MTX achieved was 45 mg/week; in 21 patients, the max dose of 45 mg/week was reached. One patient in each group achieve the primary outcome of a DAS28 of less than 3.2. Five patients in each group showed a greater than 1.2 unit improvement in their DAS28, and one patient in each group achieved an ACR20 response.

Investigators concluded that switching from PO to parenteral MTX 15 mg/week results in an improvement of disease control in some patients, and more interestingly, that increasing the dose from 15 mg/week to 45 mg/week did not improve disease control, and that for those who do not respond to the switch to parenteral, there was no benefit in escalating the dose, and an alternative strategy should be tried.

Rau and colleagues studied the radiographic outcome after 3 years of patients with early erosive RA treated with IM MTX or parenteral gold (gold sodium thiomalate-GSTM), which was an extension of a one-year double-blind study.10 One hundred seventy-four patients from two hospitals with active d and a symptom duration of at least 4 months were randomly assigned to receive MTX or GSTM treatment. Patients received either 15 mg MTX or 50 mg GSTM, administered weekly for 12 months. GSTM dosage was then reduced by half, and MTX dosage remained constant. Radiographic scores after 3 years showed that 50% of MTX and 45.8% of gold patients still had a score of less than 5% of the max, representing nearly no progression or minimal progression. During the first year of treatment, 21.4% of patients in the MTX group and 25% of the gold group demonstrated no increase in score, and there was no increase greater than the minimal detectable change in 50% of patients in the MTX group and 61% of the gold group. Both treatment groups achieved significant clinical improvement—11% of patients in both demonstrated substantial radiographic progression and reached greater than 20% of the maximum possible score after 3 years. Fifty percent had nearly no progression and reached less than 5% of the maximum possible score.
Another group looked at their registry to compare those patients who had been treated with parenteral and PO MTX and compared their outcomes. Two hundred thirteen patients who had been on a stable dose of IM MTX as of June 2001 had been switched to PO MTX from June to September 2001 because of a shortage of IM MTX.11 MTX was first switched from IM to PO, and most experienced increased disease activity. When IM MTX was available again, 47 of 143 patients were switched back, and most of the 47 experienced decreased disease activity within 3 months of resumption of IM treatment. This natural experiment of switching to PO and then switching back adds to the increasing evidence of possible better efficacy with parenteral MTX over PO MTX.

Another group studied drug survival and reasons for discontinuation of IM MTX.12 Consecutive patients with RA or other rheumatic diseases who had switched from PO to equivalent doses of parenteral MTX therapy in outpatients clinic between April 1997 and January 2004 were enrolled. One hundred thirty eight had RA. Patients had switched from PO MTX to IM MTX because of lack of efficacy of PO MTX (139/228), adverse events to PO MTX (52/228), or other reasons (13/228). Six months after IM MTX initiation, 114 were still receiving IM MTX therapy, and in addition, median CRP had decreased from 20 mg/L to 12 mg/L; the percentage of patients who had received glucocorticoids during the previous 6 weeks had decreased from 66% to 46%. After 6 months, 63 patients who had switched to IM MTX because of lack of efficacy of PO MTX had discontinued IM MTX, and 115 patients discontinued mostly because of lack of efficacy (50%) and other reasons (21%). About half of the patients benefited from IM MTX for at least 6 months regardless of the reason for switching from PO MTX, and one in five continued parenteral therapy for more than 24 months.

Discussion

Despite few RCT of parenteral versus oral MTX, the majority of the data suggest that there is an added benefit to switching from oral to parenteral MTX when there is an inadequate response to the oral version, possibly before escalating to other biologic or non-biologic combinations. The option to start MTX treatment as a parenteral drug may also have additional benefit over the oral version, with increased bioavailability,13,14 possibly less adverse events, and increased efficacy, and in certain patients more compliance. We would hope to see more RCTs where parenteral versions of MTX are used, in addition to trials where biologics are also compared to parenteral MTX to better define when we should escalate our RA therapies to include a biologic agent after MTX.

Disclosure Statement

Yusuf Yazici, M.D., is a consultant for Abbvie, BMS, Celgene, Janssen, Pfizer, Samumed, and UCB. Yasmin Bata does not have a financial or proprietary interest in the subject matter or materials discussed, including, but not limited to, employment, consultancies, stock ownership, honoraria, and paid expert testimony.

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