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ORIGINAL ARTICLE

When should we use parenteral methotrexate?

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Abstract Oral methotrexate is the benchmark against which other disease-modifying anti rheumatic drugs are measured. The use of parenteral methotrexate for those failing to tolerate or respond to oral therapy is accepted, but indications for its use and its place in the therapeutic ladder have not been fully investigated. We assessed the use of parenteral methotrexate (MTX) in our rheumatoid arthritis (RA) population and compared the characteristics of these patients to a matched group of those on oral therapy. We compared response rates to each approach using DAS 28 scores, ESR and visual analogue scales. Inferences on costs of parenteral therapy were made and predictors of response defined. We found that 10% of our total RA patient population were on parenteral methotrexate, having failed to tolerate or respond to oral therapy. Seventy-five percent of these met the criteria for the use of anti-tumour necrosis factor (TNF) agents. Overall response rates were equivalent to those obtained by responders to oral MTX. Patients on parenteral therapy were younger and were more likely to have extreme values of body mass index (BMI) than those on oral therapy. The approach was economically viable, although many patients unnecessarily attended hospital to receive their injections. We advocate consideration of parenteral MTX in all RA patients unresponsive to oral therapy prior to treatment with anti-TNF therapy. Response to parenteral therapy can be predicted by low BMI (below 22 kg/m^2), possibly as a result of malabsorption, or by high BMI (over 30) as a result of gastrointestinal intolerance. A mechanism to deliver this option through self-administration in the community should be encouraged.

Keywords Metabolism · Methotrexate · Parenteral · Remission · Response rates

Introduction

Oral methotrexate has been the mainstay in the treatment of rheumatoid arthritis (RA) for nearly two decades [1]. It has been shown to offer high levels of efficacy and tolerance over time [2]. Methotrexate remains the commonest single therapy prescribed [3] and is also part of almost all combination regimes. Drug survival remains high, with intolerance accounting for most treatment cessations in year 1, while inefficacy leads to most discontinuations in the second year of therapy [4]. With the advent of anti-TNF therapy, methotrexate remains an important agent in augmenting clinical response and reducing the risk of developing unwanted immune responses to biologic therapy [5]. Oral methotrexate is also cheap, even when factoring in the need for monthly monitoring. Its overall value for money is greater than for many of the other disease-modifying anti rheumatic drugs (DMARDs) and the anti-TNF agents [6, 7].

Intolerance of oral therapy accounts for most early treatment failures. Methotrexate is a folate antagonist, and the routine use of folic acid supplements reduces nausea to a degree [8]. The use of split dosing has also been advocated in this setting and may improve bioavailability as well as tolerance [9]. However, reflux symptoms remain a common problem limiting dosage escalation and are often a major issue in obese patients [10] where the oral dose needed to produce clinical benefit is likely to be higher.

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Oral administration also leads to variable absorption which may account for inefficacy and later treatment failures [11].

Parenteral administration, both by the subcutaneous and the intramuscular route, has been advocated and shown to be safe and effective [12]. At least half of those failing oral therapy will benefit from parenteral methotrexate [13], although this may carry its own risks as equivalent doses may lead to increased risks of pneumonitis and possibly other unintended effects [14]. The greater bioavailability, combined with better tolerance, of parenteral methotrexate, leads to higher plasma levels than that readily achieved by oral treatment in many patients [15]. This has led to the preferential use of parenteral over oral methotrexate in children with inflammatory arthritis, with a reduction in adverse events.

However, the number of adult patients prescribed parenteral methotrexate has remained small, in comparison with those treated with oral therapy. The reasons for this include cost, convenience and the difficulty in brokering local arrangements for administration with primary care trusts. Little data exists about which patients are likely to benefit most from this approach, and calculations of the financial implications are more difficult to make.

We wished to assess the efficacy of parenteral methotrexate in a population of patients who had failed oral methotrexate. We were keen to understand how best to use this treatment option and where to place it in the therapeutic ladder. The present study was therefore designed to assess the factors influencing the use of and response to parenteral methotrexate in patients with RA, in comparison with those on oral therapy. We wanted to define which factors predicted greater clinical benefit from this route of administration and to gather inference on costs to facilitate decision-making on the use of parenteral methotrexate by purchasers of care.

Methods

We studied all patients presently receiving parenteral methotrexate for RA [16] in our catchment population of 250,000 people. We have 2,300 patients with RA, suggesting a high level of disease ascertainment. We matched those on parenteral treatment to a control group of our RA patients on oral methotrexate, based on disease duration. All patients on parenteral treatment had already tried and failed oral methotrexate, as a result of intolerance, inefficacy, or both.

We assessed response rates in each group based on changes from baseline in each of the following: disease activity scores (DAS 28), visual analogue scales (VAS), and erythrocyte sedimentation rate (ESR). Mean scores before and after 6 months of treatment at stable doses were calculated and compared for both groups.

We also collected data on the body mass index (BMI) of each individual, together with the presence or absence of symptoms of gastro-oesophageal reflux disease (GORD). These data were then cross-checked with those relating to response to therapy to assess any correlation between them. The intention was to discover whether BMI or the presence of GORD might predict a better response to one or other modes of therapy. In those patients with a low BMI (below 22 kg/m^2), we recorded the presence of any other clinical features that might suggest an explanation for this.

We recorded the dose of methotrexate used in each patient, together with the use of all other DMARDs and the use of oral and parenteral steroids in each group. We also noted the reason for cessation of therapy and the number and nature of methotrexate related side effects in each group.

Finally, we calculated the inferences on costs for each approach. This allowed us to estimate the potential for cost-saving when using parenteral methotrexate as an alternative to anti-TNF therapy.

We compared mean scores for VAS, DAS and ESR at both time points between oral and parenteral therapy groups using the Mann–Whitney U test. We compared mean methotrexate doses using Student's t test. Chi squared tests were used to compare response rates to treatment between groups. We calculated differences in BMI between the two groups using analysis of variance.

Results

Of our RA population of 2,300 patients, 1,100 (48%) are taking oral methotrexate, 540 of whom take it in combination with at least one other DMARD. Therefore, 560 RA patients (24%) receive oral MTX as monotherapy. A further 110 RA patients (4.8%) receive parenteral treatment with subcutaneous methotrexate as monotherapy. By comparison, a further 92 (4%) are receiving anti-TNF therapy, usually in combination with oral methotrexate. Of those on monotherapy with parenteral methotrexate, 78 (71%) had a full data set completed for the purpose of this study, and this was compared with data from 78 patients on monotherapy with oral methotrexate with the same disease duration (mean 5 years) and baseline DAS scores. All patients on parenteral therapy had previously tried oral methotrexate, reaching a mean dose of 20 mg weekly. This had either proved inefficacious (n=38) or had caused unacceptable side effects (n=40). The commonest side effect was gastrointestinal intolerance, with nausea and reflux symptoms together accounting for most.

The mean age of those RA patients on parenteral therapy was 59 years, which was significantly younger than those on oral therapy who had a mean age of 64 years (p=0.03). The gender mix was similar at roughly 3:1 in favour of

females. Mean methotrexate dose was greater for those on parenteral therapy (22 mg weekly) compared with those on oral treatment (15 mg; p=0.01). All patients in both groups used supplemental folic acid in doses between 5 and 30 mg weekly, with a mean weekly dosage of 8 mg in each group.

Response rates in each methotrexate group were broadly comparable. VAS for pain improved to a mean of 7.0 [on a scale of 1 (worst imaginable) to 10 (none)] in each group. Baseline values were 2.2 for those on oral therapy and 4.0 in those on parenteral methotrexate, suggesting that those on parenteral therapy had previously had a limited response to oral treatment but improved as much as those who responded initially to oral therapy once the mode of administration was switched (Fig. 1).

The trend in mean ESR values was similar. Final mean values were not significantly different between those who received parental treatment and those who were on oral methotrexate (24 vs 21), although baseline values were slightly lower in the parenteral group, again in keeping with a partial response to initial oral therapy (32 vs 36; p=0.03).

The DAS data is important. Among those commencing parenteral methotrexate, 60 patients (76%) had a stable baseline DAS 28>5.1 and would have qualified for anti-TNF therapy on this basis, having failed a trial of at least 6 months of oral therapy. After 6 months of parenteral therapy, DAS scores fell by at least 1.2 in 59 patients (74%), equivalent to a response to treatment with biological agents in three quarters of patients. Forty-six patients (58%) had a 'good' or better response to parenteral methotrexate according to EULAR criteria. These responses were better than those seen in the group receiving oral methotrexate where 38 patients had an improvement in DAS score of 1.2 or greater (48%; p=0.035). Furthermore, DAS scores fell to <3.2 (low disease activity) in 27 patients (29%) on parenteral therapy, compared to 12 (16%) on oral methotrexate (p=0.02).

Mean BMI was slightly but not significantly greater in those on parenteral rather than oral therapy (28.4 vs 27.6). However, this statistic hides the fact that those patients on parenteral therapy were distributed bimodally, with most either being over or underweight. Almost all patients with very high BMI (>35) were on parenteral therapy. Among those with low BMI, parenteral treatment was again favoured (Fig. 2). Patients on parenteral therapy were more likely than those on oral treatment to have BMI below 22 kg/m^2 (30% vs 12%; p=0.038) or BMI over 30 (36% vs 19%; p=0.031).

Among those patients with a BMI of below 22 kg/m^2, a significant percentage had iron deficiency anaemia (42%). Of these, half had failed to respond to oral iron supplements but did improve their haemoglobin by a mean of 1.3 g within 1 month of receiving intravenous iron.

Not surprisingly, patients with symptoms of GORD had a higher BMI than those without (29.2 vs 26.2; p=0.015). Importantly, among those on parenteral methotrexate, the mean BMI in those achieving a reduction of at least 1.2 in DAS 28 scores after 6 months of therapy was significantly greater than in those failing to show this degree of improvement (31.0 vs 27.2; p=0.03; Fig. 3). This further suggests an effect of BMI on therapeutic response.

Inferences on costs based on our data show that, for every 1,000 RA patients, 48 would be treated with parenteral methotrexate, with 36 of these achieving a response equivalent to that seen with those responding to anti TNF therapy. Allowing for the relative costs of each, this approach equates to a saving of £306,000 (or over £300 per RA patient) annually.

Discussion

Methotrexate is the most popular DMARD used in the treatment of RA [1] but a significant number of patients still fail to respond to escalation of oral therapy and require the addition of other therapy or switching to an alternative

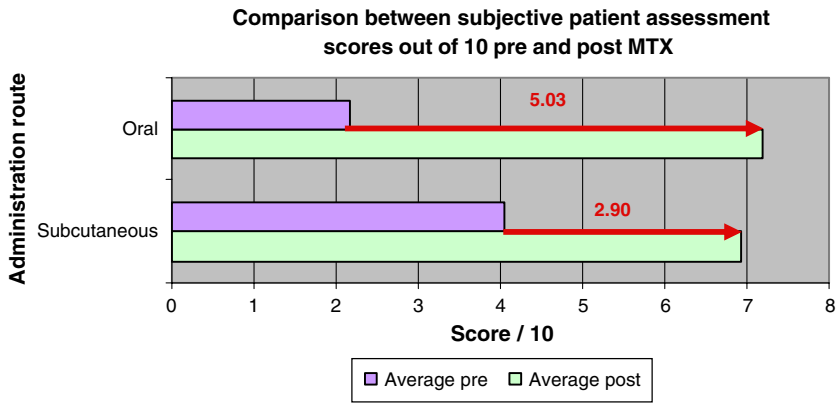

Fig. 1 Changes in mean visual analogue scores from baseline after 6 months therapy with oral or parenteral methotrexate. Scale is from 0 (worst pain) to 10 (no pain)

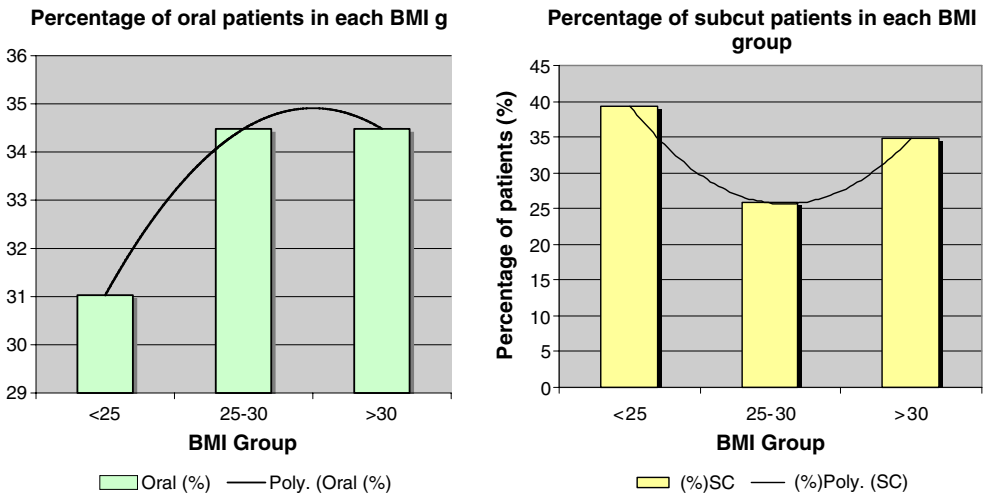

Fig. 2 Differences in distribution of BMI in patients on oral and parenteral methotrexate

therapeutic strategy [4, 17]. This paper clearly shows that in RA patients who have failed to achieve an adequate response to oral methotrexate as a result of intolerance or resistance, the majority will respond well when switched to parenteral treatment. The magnitude of this response is as good as that seen in those patients responding to oral methotrexate from the outset when assessed by improvements in VAS and ESR and is significantly better when judged more objectively using DAS 28 scores.

We found that about 5% of our total RA population were treated with parenteral therapy, approximately a tenth of those receiving the agent orally. Similar numbers of patients were taking biologics. Although those patients judged as responding to oral methotrexate were taking lower mean doses of the drug than those on parenteral therapy, patients on parenteral methotrexate had managed comparable doses of oral methotrexate without adequate response. This suggests that dose alone does not explain the difference in response rates.

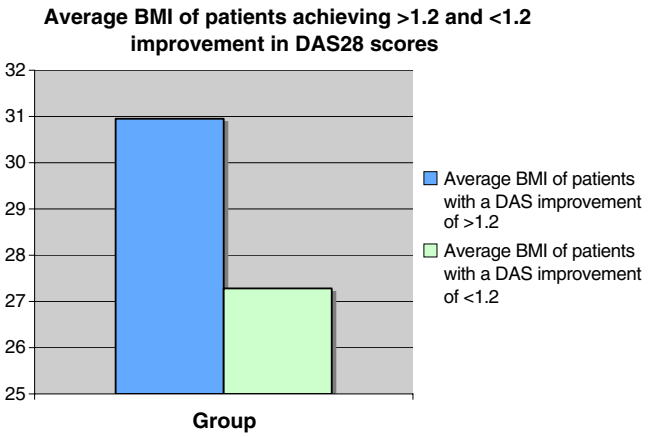

Fig. 3 Mean BMI in patients who achieved significant responses (>1.2 reduction in das) on parenteral methotrexate compared to mean BMI in those failing to respond (p=0.03)

Previous studies have reported a number of factors predicting response to monotherapy with oral methotrexate [18–21]. These have included shorter disease duration, lower levels of disease activity and lower HAQ score. Although we did not specifically study the effect of BMI as a predictor for therapeutic response to oral methotrexate, a high proportion of the patients switching to parenteral therapy were overweight, and many suffered from reflux symptoms which were the major cause of intolerance of oral treatment. The link between raised body mass index and gastro-oesophageal reflux is well-recognised [22], although it has not been previously addressed as a specific factor in defining response to methotrexate.

Our study found that patients with BMI over 30 were twice as likely to be on parenteral therapy and that almost all those with BMI greater than 35 required parenteral administration of the drug. The doses required were not excessive and were not significantly greater than the same patient group had achieved orally. Tolerance and efficacy were both very good in these patients, with DAS response rates significantly better than those achieved by patients on oral therapy. Indeed, the mean BMI in those achieving an improvement of >1.2 reduction in DAS score was significantly greater than in those who did not.

Obesity is an increasing problem in our population at large, and patients with RA are especially at risk if they feel obliged to adopt a more sedentary lifestyle as a result of their disease. Raised BMI increases loading on weight-bearing joints and may predispose to increased joint damage. If associated GORD limits patient tolerance of oral therapy, this may further reduce the influence of methotrexate on disease outcome. Clinicians may therefore wish to consider ascertaining BMI and the presence of GORD prior to commencement of methotrexate in patients with RA. Those with a BMI over 30 and symptoms of GORD may respond better to parenteral methotrexate

administration which may be more rapidly effective than oral therapy in this setting.

The bimodal distribution of BMI in those on parenteral methotrexate raises the issue of why patients receiving parenteral methotrexate were much more likely to have a BMI of below 22 kg/m^2 than those on oral therapy. It is possible that poor drug absorption may be important, and this is supported by the observation that a relatively high proportion of these patients were iron-deficient and had failed to respond to oral iron replacement. This suggests that those patients with low BMI may suffer from malabsorption, although this study did not further explore that possibility. It would appear worth taking a focussed gastrointestinal history from all patients with RA in whom methotrexate therapy is being considered.

Much effort has been directed towards the potential for predicting an individual's response to methotrexate [23, 24] with contradictory evidence on the ability of different alleles to predict both response to and toxicity from the drug [25, 26]. At present, no confident means of predicting an individual's response to treatment has been shown on the basis of their genetic profile, but simple clinical assessment including the BMI may prove useful in the interim

There are some potential drawbacks in our methodology. The study was retrospective and treatment decisions were largely clinician-led rather than protocol-guided. However, patients were given the option of biologic treatment where they met the criteria for this, although, by definition, all those in this study elected to try parenteral methotrexate before biologics.

Response to parenteral therapy may have been enhanced by better compliance with treatment, given the greater risk of adverse events with oral therapy. This is likely to have contributed to the favourable economics associated with this approach.

Our data show that 59 of the 78 patients in whom the efficacy of parenteral therapy was assessed would have met criteria for the use of anti-TNF therapy at baseline and that most of these patients responded sufficiently well to parenteral methotrexate after 6 months of therapy to avoid the need for biologic therapy. This equates to a considerable cost-saving and further reinforces the logic of trying parenteral methotrexate prior to anti-TNF therapy in those who fail to respond to oral therapy.

Summary

Parenteral methotrexate is well-tolerated and effective in most RA patients who have failed to tolerate or respond to oral therapy. The level of response is equivalent to that achieved with anti-TNF therapy. Side effects were generally minor and occurred no more often than with oral methotrexate in an unselected RA population. We strongly advocate the use of parenteral methotrexate therapy before using anti-TNF in patients with RA failing oral treatment and suggest that many such patients may be at the extremes of the BMI range.

Disclosures None

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