Methotrexate: optimizing the efficacy in rheumatoid arthritis

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***Abstract*:** Methotrexate (MTX) is currently the most frequently used drugs in the treatment of rheumatoid arthritis (RA). The drug had been synthesized in 1948 and first tests to treat patients with psoriasis and RA were published in 1951. However, until the 1980s there was only limited use of MTX in the treatment of RA. Since the 1990s MTX is the disease-modifying antirheumatic drug (DMARD) of first choice for the treatment of RA in most countries worldwide. By definition, DMARDs in RA are those compounds for which an inhibiting effect on radiographic progression has been demonstrated. Several combinations of DMARDs have been tested, most commonly with MTX as the anchor drug. Regarding the route of administration of MTX there is some evidence that the parenteral route, most often performed subcutaneously, has some additional benefits over the oral route. In MTX monotherapy, dosages up to 30 mg/week are now used. There are now three main combinations that are playing an important role: MTX + sulfasalazine (SSZ) + hydroxychloroquine, MTX + leflunomide (LEF), and MTX + biologics such as antitumour necrosis factor (anti-TNF) and other new compounds which block the interleukin 6 (IL6) receptor or T-cell activation and delete B cells. Regarding clinical efficacy, MTX monotherapy has performed almost similarly well in comparison with biologic monotherapy, both usually combined with glucocorticoids. However, structural damage is usually inhibited to a significantly greater degree with the biologics. The combination of MTX with biologics has proven superior to either agent alone in all aspects. Current strategic regimens which concentrate on systematic ways to bring patients into remission all include MTX as first choice.

***Keywords*:** combination therapy, DMARDs, methotrexate, monotherapy, rheumatoid arthritis, therapeutic strategies

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Introduction

Methotrexate (MTX) is currently the most frequently used drug in the treatment of rheumatoid arthritis (RA). The drug was first synthesized as a less toxic alternative to aminopterin [Smith *et al.* 1948] and used in the treatment of malignancy. Some years after aminopterin had been tested with some success in patients with psoriasis and RA as early as in 1951 [Gubner *et al.* 1951], MTX was tested and found to be less toxic than aminopterin [Edmundson *et al.* 1958]. However, until the 1980s there was only limited use of MTX in the treatment of RA. Thereafter MTX was increasingly used, and many trials have investigated the properties, efficacy and toxicity of this compound in patients with RA. Since the 1990s MTX is the disease-modifying antirheumatic drug (DMARD) of first choice for the treatment of RA in most countries worldwide. It has also been called the anchor drug [Pincus *et al.* 2010] since most trial designs relate to response to MTX. This review is not based on a systematic literature search, but rather tries to give an overview based on examples of clinical studies. Thus, the references listed are incomplete.

Comparison of methotrexate with other DMARDs

By definition, DMARDs in RA are those compounds for which an inhibiting effect on radiographic progression has been demonstrated. Comparisons of MTX with other DMARDs suggested that MTX is probably more efficacious. However, there are some methodological problems with comparisons, one of which is that in most of the early trials rather low dosages of MTX were used.

In a multicentre, double-blind trial, 999 patients were randomized to leflunomide (LEF) or oral MTX for 52 weeks [Emery *et al.* 2000]. Treatment with MTX resulted in better results for tender and swollen joint counts, physician and patient global assessments, and erythrocyte sedimentation rate (ESR).

In a comparative study with oral gold and low-dose oral MTX, both medications showed significant improvement in all clinical parameters [Weinblatt *et al.* 1990]. However, the beneficial effects appeared earlier and the rates of improvement were stronger with MTX (e.g. improvement in terms of tender and swollen joints in 70% with MTX and in 41% with oral gold), while discontinuations due to adverse effects occurred in 22% of patients on therapy with gold and in 7% on MTX. For comparison, discontinuations due to lack of efficacy were observed in 2.9% in the MTX and in 9.1% in the oral gold group, respectively. The results of the trials comparing parenteral gold to oral MTX revealed similar results. In a Canadian double-blind randomized trial, 18 patients with active RA were treated with 12.5 mg oral MTX and 17 patients with 50 mg parenteral gold for 6 months. The patients improved significantly but there was no major advantage for MTX [Morassut *et al.* 1989]. In another Canadian trial 20 patients were treated with 10mg oral MTX and 50 mg aurothiomalate, respectively [Suarez-Almazor *et al.* 1988]. In a German trial, 87 patients were treated either with intramuscular MTX or aurothiomalate [Rau *et al.* 1991]. Discontinuations due to adverse effects were significantly higher in the gold group as well as the severity of adverse effects (74.7% *vs.* 48.3%). Clinical parameters improved in both groups with no significant difference between the compounds.

The efficacy of oral MTX and azathioprine (AZA) was compared in a 48-week randomized double-blind trial [Jeurissen *et al.* 1991]. The discontinuation rate because of adverse effects and lack of efficacy was significantly higher in the AZA group. After 48 weeks only 36% of patients on AZA but 91% on MTX were still receiving the medication. The improvement of tender joint count and ESR after 24 and 48 weeks was significantly better in the MTX group. In a systematic comparison, the traditional DMARDs have recently been compared regarding efficacy and safety [Aletaha *et al.* 2002]. MTX was the most commonly administered drug in patients with RA (29.5%), followed by chloroquine (21.6%). Reasons for discontinuation of DMARD therapy were (i) insufficient efficacy (37%), (ii) subjective side effects (29%), (iii) abnormalities of laboratory parameters (8%) followed by (iv) objective side effects. MTX had the highest retention rate of all tested conventional DMARDs (median drug survival time 40 months) while the lowest retention rate was found for cyclosporine (median drug survival time 13 months). Combinations of several DMARDs did not differ significantly from MTX. In the combined analyses of efficacy and toxicity, MTX and sulfasalazine (SSZ) performed best, chloroquine was not much different.

Combination therapies with conventional DMARDs

Several combinations of DMARDs have been tested most commonly with MTX as the anchor drug. There are now mainly three combinations that are playing an important role: MTX + SSZ + hydroxychloroquine (HCQ), MTX + LEF, MTX + biologicals. The combination of MTX, SSZ and HCQ was investigated the first time by O'Dell *et al.* [O'dell *et al.* 1996]. In a 2-year double-blind randomized controlled study 102 patients who had shown an insufficient response to at least one DMARD were treated either with MTX alone, SSZ plus HCQ or a combination of all three drugs. This latter combination turned out to be significantly more effective than the other two regimens with no higher toxicity. An American College of Rheumatology (ACR) improvement of 50% was observed in 50/102 included patients (50%), 77% of which had been treated with all three drugs, 33% with MTX alone, and 40% with a combination of SSZ and HCQ. However, the dropout rate was rather high (51%), mainly due to a lack of efficacy. In another trial which compared monotherapy with combination therapy, much lower dropout rates were reported [Calguneri *et al.* 1999]. There were three groups with a total of 180 patients: group I was treated with only one of the three drugs, group II received a combination of either MTX + SSZ or MTX + HCQ, and group III was treated with a combination of all three agents. After 2 years a >50% improvement of clinical and laboratory parameters was achieved in 49%, 73% and 87%, and remission was reported in 31%, 45% and 60%, respectively. Importantly, patients in group III did not show more adverse effects

than those in the other groups [Calguneri *et al.* 1999].

The combination of these three drugs was also tested in Finland [Mottonen *et al.* 1999] with a dynamic study design: depending on the clinical response the dosage was increased. The control group was initially treated with SSZ alone; this could be substituted by MTX or other DMARDs in cases of unresponsiveness. After 2 years 37% and 18% of the patients from the combination and the monotherapy group were in remission, respectively. The ACR 50 response rates were also superior with the combination therapy [Mottonen *et al.* 1999].

Since MTX and LEF have complementary mechanisms of action, the combination of both drugs was a logical step. In a small open study, 30 nonresponders to MTX were treated with a combination of LEF and MTX for 52 weeks [Weinblatt *et al.* 1999]. As usual, stable doses of nonsteroidal anti-inflammatory drugs (NSAIDs) and prednisone could be administered in addition. The combination demonstrated significant clinical improvement (53% achieved ACR 20) without major toxicity problems [Weinblatt *et al.* 1999]. In another study in which the combination of LEF + MTX was compared with MTX + placebo in patients that had not sufficiently responded to MTX-monotherapy, 46.2% *versus* 19.5% achieved ACR 20 improvement [Kremer *et al.* 2002].

Taken together, there is some evidence that the combination of conventional DMARDs is more efficacious than monotherapy. However, it does not seem necessary to treat all patients with RA in a more intensive way.

Combination therapies with biologics

The combination of MTX with biologics has always been superior when compared with either of those medications alone. The majority of the trials have concentrated on patients with an insufficient response to MTX. In many studies this has just been defined subjectively, and this may explain some variance in trial results. However, there are also some studies in MTX-naïve patients: a rather different patient population.

In a pioneer study in juvenile idiopathic (poly)arthritis (JIA) the efficacy of combining MTX with the 75 kD tumour necrosis factor (TNF) receptor fusion protein etanercept (ETN) was higher than MTX + placebo in patients who had been resistant to MTX [Lovell *et al.* 1999]. After 24 weeks ACR 20 and ACR 50 responses were achieved by 71% and 39% of these patients while only 27% and 3% of the placebo group reached those levels, respectively. These response rates were sustained for a 2-year period (median), and many patients could either reduce or completely discontinue the concomitant corticosteroid medication. The combination of infliximab (INF) with MTX also demonstrated good efficacy and safety in adult patients with severe RA: about 60% of the patients achieved a major improvement [Elliott *et al.* 1994]. Clinical and radiological success of the combination of MTX and infliximab could be shown for a treatment period of 2 years [Maini *et al.* 2001]. Moreover, the combination of MTX with TNF blockers generated a better tolerance towards the antibodies which reportedly occur with INF and adalimumab (ADA) therapy [Bartelds *et al.* 2010, Jamnitski *et al.* 2011]. Similar data have been published for the other TNF blockers ADA [Van Der Heijde *et al.* 2010], golimumab [Kremer, 2010] and certolizumab [Mease, 2011], the IL6 receptor antagonist tocilizumab [Burmester *et al.* 2010], the B-cell depleting agent rituximab [Tak *et al.* 2010] and the T-cell costimulation inhibitor abatacept [Maxwell *et al.* 2010].

Taken together, regarding clinical efficacy MTX monotherapy performs almost similarly well in comparison to biologic monotherapy, both usually combined with glucocorticoids [Rau, 2010]. The combination of MTX with biologics is always superior to either monotherapy. Biologics have better efficacy regarding radiographic damage.

Radiographic progression

In addition to clinical improvements in disease activity and function, radiographic damage and progression is a very important criterion to judge on the efficacy of DMARDs. There are only a limited number of trials that fulfil essential methodological requirements. Several smaller open and retrospective studies with MTX suggest a positive effect of the drug and seem to slow down the destructive course of the disease [Kremer and Lee, 1986]. In a German study with 174 patients with early erosive RA a significant retardation of radiographic progression was found in both groups after 1 year of therapy

[Rau *et al.* 1998]. In a 5-year trial with 60 patients there was significantly less radiographic progression in the patients treated with MTX as compared with penicillamine. Half of the MTX-treated patients showed no radiographic progression some of which were in clinical remission [Drosos *et al.* 1997]. The radiographic progression of RA patients treated with either AZA or MTX showed that after 6 and 12 months, fewer patients in the latter group had developed new erosions [Jeurissen *et al.* 1991]. The radiographic course of RA was studied in patients before and after low-dose MTX pulse therapy. While clinical parameters (morning stiffness, pain and ESR) improved significantly, no significant differences in the development of erosions before and after that treatment were observed. In another study the authors calculated that MTX treatment decelerated the radiographic course of patients with RA by a factor 3 [Alarcon *et al.* 2000].

Taken together, there is no reasonable doubt that MTX does decelerate the radiographic progression in patients with RA [Rau, 2010]. However, MTX does not stop radiographic damage in severe RA. As already pointed out, all biologic agents have been shown to increase the efficacy of MTX with regard to the inhibition of radiographic damage [Rau, 2010].

Bioavailability and routes of administration

MTX as monotherapy or in a combination with other drugs, including glucocorticoids and biologics, is the most common treatment for RA patients in the world today, and MTX is considered the anchor drug for the vast majority of therapeutic strategies [Pincus *et al.* 2010]. Although the oral route of administration of MTX is still the most frequently used, there is an increasing tendency to choose the subcutaneous route of administration. The rationale for that is that the bioavailability of oral MTX is rather variable (50–80%) and several trials have demonstrated that the bioavailability of subcutaneous MTX is superior [Nam *et al.* 2010]. Indeed, some clinical studies have also proposed to use subcutaneous MTX as a reasonable alternative and to switch from the oral to the parenteral route of administration [Jundt *et al.* 1993]. In general, food intake has no major effect on the bioavailability of low dose MTX in patients with RA [Rozin *et al.* 2002]. However, although the peak concentration of MTX is not reduced by the intake of food, the time to reach the highest concentration seems slightly longer. In a retrospective chart review of polyarticular juvenile RA (JRA) and RA patients, an equal efficacy of oral, subcutaneous and intramuscular ways of administration was reported. Furthermore, the parenteral routes were tolerated better and fewer gastrointestinal side effects were observed [Oguey *et al.* 1992]. However, taken together there is no data that convincingly prove that parenteral MTX is associated with less gastrointestinal tract side effects in comparison to the oral route. Clinical experience tells that this is rather variable which indicates that there are patients who tolerate tablets better than injections and the other way round.

The role of absorption limitation of MTX has been studied by Hoekstra and colleagues [Hoekstra *et al.* 2006] by comparing the bioavailability of a divided higher (25–35 mg weekly) oral dose of MTX in comparison with a single dose in 10 adult patients with RA. The bioavailability of the split dose was 28% higher compared with the single-dose group with a median weekly oral dose of 30 mg MTX. Compared with a historical subcutaneous control group the relative bioavailability was 0.76 and 0.9 for the single dose and the split dose group, respectively. Thus, when higher MTX doses are needed, splitting the oral dose may be an option and a suitable alternative for subcutaneous administration.

Dosage and response to methotrexate

Many studies have tried to explain and identify indicators of a good response to MTX therapy. From the pharmacological point of view, MTX is an antifolate prodrug, metabolized by polyglutamate synthetase into MTX polyglutamates (PGs): this leads to the addition of 2–7 glutamic residues to the parent drug. These MTXPGs are metabolites which are produced in different forms (length). Dependent on the number of residues short- or long-chain MTXPGs arise, and this may have an influence on clinical efficacy and tolerability. Analysing the accumulation of different MTXPGs in erythrocytes in correlation to the effect of switching from oral to parenteral MTX in 10 RA patients with insufficiently controlled disease activity showed an increase of MTXPGs [Robbins *et al.* 1997]. The authors hypothesized that this accumulation of long-chain MTXPGs may be the reason for an increased efficacy of MTX. Similar results were reported in patients with JIA ($n = 99$); the subcutaneous route of administration was also associated with higher proportions of intracellular

long-chain MTXPG [Becker *et al.* 2010]. Since a study on dose escalation of oral MTX in patients with RA also showed a selective distribution toward intracellular long-chain MTXPGs [Dervieux *et al.* 2010] it appears that the selective emergence of these active metabolites may be mainly a function of dose intensity.

Somewhat different results came from a recent multicentre study with a total of 256 patients who received low-dose MTX for at least 3 months [Dervieaux *et al.* 2010]. A large interpatient variability in MTX dosing (range 5–25 mg/week) and MTXPG accumulation was found. The most impressive result was that the increase of $MTXPG_3$ levels was associated with 25-fold higher likelihood of a response to MTX. Furthermore, the addition of glutamic residues appeared to even enhance the efficacy.

Taken together, these interesting results should lead to further studies on the subject.

Efficacy of subcutaneous methotrexate

Several studies have been performed but only one was powered enough to directly compare the clinical efficacy and tolerability of oral *versus* subcutaneous MTX: a randomized, double-blind, placebo-controlled, multicentre study recently performed in Germany with 384 MTX-naïve active early RA patients (DAS28 $\geq$ 4) who were randomly assigned to either oral MTX (15 mg given as two 7.5 mg tablets plus dummy prefilled syringe) or subcutaneous MTX (15 mg as prefilled syringe at 10 mg/ml plus dummy tablets) for 4 months [Braun *et al.* 2008]. At week 16, ACR20 nonresponders were switched from oral MTX to 15 mg subcutaneous and from 15 mg subcutaneous to 20 mg subcutaneous for the remaining 8 weeks. In addition patients received 5 mg folic acid given 24 h after MTX. The parenteral route of administration was more successful than the oral form in almost all analyses after 4 months. After treatment for 6 months, 34% (subcutaneous) *versus* 24% (oral) of the patients were in remission, respectively: a relative increase of 42%. More than 50% of the patients reached 'good' improvement (EULAR criteria) when receiving subcutaneous MTX: an increase of 30% compared with tablets. This study clearly showed that, at the same dose level, the subcutaneous application is more efficacious than the oral route [Braun *et al.* 2008]. A direct comparison of treatment strategies with an increased oral dosage has not been performed so far. It would be especially interesting to learn whether a higher oral dose of MTX will lead to less side effects while potentially being as efficacious as a lower dose given parenterally [Braun, 2010].

Addition of folic acid

Since some MTX toxicities can be interpreted on the basis of folate deficiency, supplementation strategies with various folates have been studied. On the other hand, excessive doses of folinic acid can negate MTX efficacy in RA, however more moderate doses of both folic acid and folinic acid have been shown to reduce toxic manifestations (for a review see Morgan *et al.* [2010]). Overall, the question of whether or to what degree folate supplementation may affect MTX efficacy has still not been completely answered. One reason for this is that it is a complicated issue; for example, one interpretation of the data is that folic acid supplementation allows a higher dose of MTX to be tolerated, thereby increasing its efficacy. Furthermore, folic acid supplementation was shown to have a favourable effect on homocystein metabolism and may have other effects on MTX metabolism such as lowering the formation of less active metabolites such as 7-OH-MTX [Morgan *et al.* 2010]. The optimal dosing regimen for folic acid and folinic acid is as yet unknown and without reasonable doubt a balance between MTX, and folate dose is important. In general, there seems to be a broader margin of safety using folic acid. Furthermore, the lower cost does argue for folic acid. The potential of folic acid interfering with MTX absorption can be overcome by giving it 24 hours prior to the weekly MTX dose or 24 hours following the dose [Morgan *et al.* 2010].

Summary

MTX is still very much at the centre of all therapeutic strategies for RA and other rheumatic diseases. MTX is frequently combined with NSAIDs and corticosteroids, other conventional DMARDs and biologics. The latter clearly enhance the efficacy of MTX, especially regarding the inhibition of radiographic progression. The parenteral way of administration of MTX is superior to the oral route, presumably because of the better bioavailability. There is also data to support a role of intracellular MTX polyglutamates in that regard. Whether increasing the oral dosage leads to similar clinical effects without increasing the toxicity remains to be shown.

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