Optimal administration and dosage of methotrexate

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ABSTRACT

Methotrexate (MTX) has been used for the treatment of rheumatic diseases, especially rheumatoid arthritis (RA), for some decades now. Although it had been known from pharmacokinetic studies for quite some time already that the bioavailability of MTX is superior when administered parenterally rather than orally, this had never been formally proven to be clinically relevant. In a recent randomised clinical trial, the two ways of administration have been directly compared. The fact that the patient group that received MTX s.c. had better clinical outcome than the oral group can be considered as proof that this hypothesis has now been confirmed. Although this result does not mean that every patient will be in need of parenteral administration of MTX, it suggests that very active patients and those with a worse prognosis may have more benefit from this strategy.

Introduction

Methotrexate (MTX) was developed initially as an antimetabolite agent to treat neoplastic diseases and to suppress undesired immunological activities. MTX inhibits purine nucleotide and thymidylate synthesis and, subsequently, inhibition of DNA and RNA syntheses (1, 2). The mechanisms of action are discussed elsewhere in this supplement (3).

First reported for treatment of rheumartoid arthritis (RA) in the early 1950s, soon after its development (4), MTX did not come into common use in the treatment of RA until more than 30 years later (5-9). As an antirheumatic agent, MTX is administered intermittently (weekly) in doses two or three log orders lower than those required for the treatment of malignancy (5–25 mg/week *vs*. 5000 mg/week).

MTX is widely used to treat inflammatory rheumatic diseases; several examples are presented and discussed in this supplement. This paper focuses on rheumatoid arthritis (RA) – the most frequent inflammatory rheumatic disease and the one which has been extensively studied in the last decades. The latter statement includes the number of studies on MTX which is given as monotherapy, as combination therapy with other disease modifying anti-rheumatic drugs (DMARDs) and/or with biologic agents such as TNF blockers, IL-1, IL-6, and B- or T-cell inhibitors. When initiated early in the course of the disease, MTX is nearly as effective as biologic agents for RA (10), and is commonly administered in combination with either biological agents or other small molecule antirheumatic drugs. MTX is considered the anchor drug in the treatment of RA (11). No novel drug is currently approved without a study that has some relation to MTX – either with a design concentraing on MTX- non- or insufficient responders, or in MTX-naive patients with RA, in early, established or advanced disease stages, patients being rheumatoid factor and/or anti-CCP antibody –positive or negative. This paper is mainly based on evidence derived from monotherapy studies.

Short- and long-term efficacy of methotrexate in rheumatoid arthritis

In one of the early studies with 189 patients over 18 weeks MTX was clearly superior to placebo, with only 3% dropping out due to inefficacy in the MTX *vs*. 21% in the placebo group (12). Later, it was shown that the effects of MTX showed a roughly linear dose relationship. During this 16-week trial (13) patients were treated with different doses (5mg/m^2 or 10mg/m^2 corresponding to approximately 17.5mg/m^2/week) of MTX compared to placebo. A meta-analysis of the placebo-controlled trials (14) showed average improvements in efficacy of 25–40% for MTX compared to placebo. Studies on the long term efficacy of MTX demonstrated sustained efficacy for several years. Observation

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periods of 12 years and more were published (15). In a prospective long-term study 25 out of the initial 29 patients (86%) were still on MTX therapy after nearly 5 years, and after almost 8 years the proportion was still 62% (16). The MTX retention rate can be expected around 50% at 5 years (16). The beneficial effects of MTX usually appear within weeks of its administration, and NSAIDs and/or corticosteroids are used as bridging therapy.

Treatment with MTX reduces mortality (17, 18). In patients with severe RA who did not respond to MTX, the standardised mortality ratio (SMR) was more than 4-fold increased compared to the general population (17). In a prospective study, the cardiovascular mortality of 1240 RA patients was reduced when they had been treated with MTX (18).

Patients with RA are generally more likely to discontinue MTX because of side effects than because of inefficacy. The concomitant administration of folic or folinic acid may decrease the toxicity of MTX (19). This topic is discussed elsewhere in this supplement (20).

Patients taking MTX must get appropriate laboratory tests done (blood cell counts, hepatic enzymes, creatinine) - initially every 2, later on every 4–12 weeks. Especially older people need to be monitored carefully to recognise serious side effects in time (21). As currently used, for the treatment of RA and other rheumatic diseases, MTX in relatively low doses of <30mg/week is safe and well tolerated. Because of its efficacy and safety, MTX is now first-line therapy for the treatment of RA (21-23). Whether combination therapy of conventional DMARDs with MTX is superior to monotherapy seems not entirely clear (24, 25), but the combination of MTX with biologics is clearly better than monotherapy with either agent (26).

Ways of administration of methotrexate in relation to bioavailability

MTX can be taken orally or administered by subcutaneous (s.c.), intramuscular (i.m.), intravenous (i.v.) or intrathecal injection. Although daily preparations are occasionally used, most patients take weekly doses, which works generally well and decreases the risk of side effects (27). This issue is handled in depth elsewhere in this supplement (28).

The half-life of MTX in the serum is in the range of 6–8 h after administration of the drug and is undetectable in the serum by 24h. However, at the doses commonly used for the treatment of RA, the bioavailability of oral MTX varies considerably between individuals, but in general is in the range of 70%, and food does not significantly affect uptake of the drug (29-32). There is some evidence that at higher doses oral bioavailability declines, a phenomenon most likely due to the fact that uptake of MTX from the gastrointestinal tract is mediated by a saturable transporter, reduced folate carrier 1 (RFC1; 33). Thus, explanations for the difference in bioavailability after oral or parenteral administration of MTX can be found in either the absorption limitation (34) or a first-pass effect. The inverse relation between oral dose and bioavailability suggest an important role for absorption limitation (28).

The route of MTX administration was shown to contribute to differences in bioavailability in a recent study on patients with juvenile arthritis in which the intracellular concentration of polyglutamates (PG) varied 40-fold (35). Individual MTX glutamate metabolites (MTXGlu (1-7) were detected –with one subtype being the predominant contributor (MTXGlu3) to the variability in concentrations of the MTX metabolites (36). However, MTX-PG are, in general, less suitable indicators of MTX bioavailability, because their steady state concentrations are reached only after several months of stable dosing, assuming patient compliance to MTX intake (36). Although no absolute correlation of MTX-PG levels with efficacy have been found, patients with MTXPG levels above 60 nmol/l seem more likely to have a therapeutic benefit than those patients with lower levels, while adverse events seem to occur independent of that. However, due to considerable overlap between patients and groups, the utility of this measurement in clinical practice is rather limited. Moreover, the lag to steady state equilibrium diminishes the timeliness necessary if this were to be used to guide dose escalations. Furthermore, recent studies show inconsistent associations between MTX-PG concentrations in erythrocytes and disease control (37).

Important interactions of methotrexate

MTX is primarily excreted in the urine, although there is some biliary excretion. By decreasing glomerular filtration rate, nonsteroidal anti-inflammatory drugs (NSAIDs) may increase the time required to eliminate MTX, although this interaction is of little or no clinical significance (38). NSAIDs modestly diminish renal clearance of MTX and its major metabolite 7-hydroxymethotrexate, although this interaction is generally not clinically significant (39-46).

NSAIDs, corticosteroids, and various other second-line agents are generally taken by almost all patients with active RA. More recently, combinations of MTX with other second-line agents (sulfasalazine, hydroxychloroquine, anti-TNF agents, and other biologicals) have been reported to have greater efficacy than MTX alone without greater toxicity (47-53). Hydroxychloroquine alters the pharmacokinetics of MTX; there is slower clearance and uptake with a greater area under the curve for MTX in patients taking the combination (54), and this interaction may account for the greater efficacy of the combination of hydroxychloroquine and MTX than MTX alone (48, 49). Leflunomide, a second-line small molecule therapy for RA which inhibits pyrimidine synthesis, has been safely used in combination with MTX, although severe liver and bone marrow toxicity have been reported with the combination (55-60).

Folate deficiency

Folic acid, or vitamine B9, is composed of a pterin ring connected to p-aminobenzoic acid (PABA) and conjugated with one or more glutamate residues. It is distributed widely in green leafy vegetables, citrus fruits, and animal products. Humans do not gener-

ate folate endogenously because they cannot synthesise PABA, nor can they conjugate the first glutamate. Folates are present in natural foods and tissues as polyglutamates because these forms serve to keep the folates within cells. In plasma and urine, they are found as monoglutamates because this is the only form that can be transported across membranes. Enzymes in the lumen of the small intestine convert the polyglutamate form to the monoglutamate form of the folate, which is absorbed in the proximal jejunum via both active and passive transport (61).

Within the plasma, folate is present, mostly in the 5-methyltetrahydrofolate (5-methyl THFA) form, and is loosely associated with plasma albumin in circulation. The 5-methyl THFA enters the cell via a diverse range of folate transporters with differing affinities and mechanisms (*i.e.* adenosine triphosphate (ATP)–dependent H^+ cotransporter or anion exchanger). Once inside, 5-methyl THFA may be demethylated to THFA, the active form participating in folate-dependent enzymatic reactions. Cobalamin (B-12) is required in this conversion, and in its absence, folate is trapped as 5-methyl THFA (61). From then on, folate no longer is able to participate in its metabolic pathways, and megaloblastic anemia results.

The biologically active form of folic acid is tetrahydrofolic acid (THFA), which is derived by the 2-step reduction of folate involving dihydrofolate reductase. THFA plays a key role in the transfer of 1-carbon units (such as methyl, methylene, and formyl groups) to the essential substrates involved in the synthesis of DNA, RNA, and proteins. More specifically, THFA is involved with the enzymatic reactions necessary to synthesis of purine, thymidine, and amino acid. Manifestations of folate deficiency thereafter, involve impairment of cell division, accumulation of possibly toxic metabolites such as homocysteine, and impairment of methylation reactions involved in the regulation of gene expression, thus increasing neoplastic risks (61).

A healthy individual has about 500-20,000µg of folate in body stores. Humans need to absorb approximately 50-100µg of folate per day in order to replenish the daily degradation and loss through urine and bile. Otherwise, signs and symptoms of deficiency can manifest after 4 months (61).

The current standard of practice is that serum folate levels less than 3ng/mL and a red blood cell (RBC) folate level less than 140ng/mL puts an individual at high risk of folate deficiency. The RBC folate level generally indicates folate stored in the body, whereas the serum folate level tends to reflect acute changes in folate intake (61).

Data from the National Health and Nutrition Examination Survey (NHANES) 1999–2000 indicate the prevalence of low serum folate concentrations (<6.8nmol/L) decreased from 16% before folic acid fortification to 0.5% after folic acid fortification (62).

Folate in the 5-methyl THFA form is a cosubstrate required by methionine synthase when it converts homocysteine to methionine. As a result, in the scenario of folate deficiency, homocysteine accumulates. Several recent clinical studies have indicated that mild-to-moderate hyperhomocystinemia is highly associated with atherosclerotic vascular disease such as coronary artery disease (CAD) and stroke (63).

Folate deficiency can result from several possible causes, including inadequate ingestion, impaired absorption, impaired metabolism leading to inability to utilise folate that is absorbed, increased requirement, increased excretion, and increased destruction.

Whether a generally screening for folate deficiency is useful to decrease MTX toxicity is unknown.

Optimal administration of MTX

As recently proposed (22), all patients with RA should take as high a dose of weekly MTX as needed or tolerated (up to 25–30mg). In a systematic literature search (up to September 2007) a total of 38 publications out of 1,748 identified references were finally selected to undergo further analysis (27). On that basis, the optimal evidence based dosing and routing recommendation for MTX in RA was to start on MTX 15mg/week orally, escalating with 5mg/ month to 25–30mg/week, or the highest tolerable dose, with a subsequent switch to subcutaneous administration in the case of an insufficient response (24).

Switching from oral to parenteral MTX in insufficient responders has already been proposed some years ago (64), and loss of response has been observed in patients in remission who switched from parenteral to oral MTX (65). Another possibility proposed is to split the dose because of the already discussed limited bioavailability with higher dosages (28, 66).

In the 3E Initiative (evidence, expertise, exchange) 751 rheumatologists from 17 countries participated to develop evidence-based recommendations for the use of MTX in daily clinical practice based on the literature search already mentioned (23, 27). A total of 10 recommendations for the use of MTX in daily clinical practice focussed on RA were developed. Parenteral administration of MTX of 20–30 mg/week depending on clinical response and tolerability was recommended – as was rapid dose escalation of 5mg/month to 25–30 mg/week being associated with higher efficacy, but also with more adverse events, in comparison with slow escalation of 5mg/3 months.

Until recently, oral *vs.* s.c. administration of MTX has been considered equivalent in the treatment of RA, although it had been known for some time that the bioavailability of parenteral MTX is superior (29-32) making this route of administration potentially preferable to the oral route – at least in certain patients. The findings of the first and so far only multi-centre, prospective, randomised, blinded trial (67) of oral *vs.* s.c. MTX in MTX- and biologic naive patients with RA and high disease activity (defined as a DAS28 >4) have shown that the s.c. administration suggest indeed that the s.c. administration is superior. Patients were blindly randomised to one of two groups: oral MTX 15mg/ week + placebo injection, and s.c MTX 15mg/week + oral placebo. Subjects were continued on stable background NSAIDs and low-dose prednisone. Folic acid was administered to all subjects at a dose of 5mg/week. The primary outcome measure was the ACR20 response at 24 weeks, with ACR50 and 70, DAS28,

Table I. Results of the direct comparison of oral *vs*. s.c. MTX.

	oral MTX n=187	s.c. MTX n=188	*p*-value
ACR20	70%	78%	0.005
ACR50	59%	62%	NS
ACR70	33%	41%	<0.05
EULAR Remission	24%	34%	<0.05

EULAR response criteria, and time to ACR20 as secondary outcome measures. A rescue arm was utilised, such that subjects in the po MTX group who had not achieved an ACR20 response by week 16 were blindly crossed over to the s.c. MTX group (n=30). Subjects in the s.c. MTX group not achieving an ACR20 response at 16 weeks had their s.c. MTX dosage increased to 20mg/week (n=22). A total of 384 subjects were randomised to the oral – (n=187) and s.c.-MTX (n=188) groups, respectively. Subjects were primarily female (75%), mean age 59 years, short disease duration of 2–3 months and high baseline disease activity (mean DAS28 >6.0). The 24 weeks of the study were completed by 89% of the enrolled subjects. All efficacy endpoints tended to favour the s.c. MTX arm, two of them significantly.

Of note, there was no difference in safety or toxicity between the two groups.

These overall excellent treatment responses achieved with relatively moderate doses of MTX highlight the potency of this DMARD. Overall, the results suggest to rather choose s.c. over oral MTX in patient groups. However, the oral administration was also very efficacious in almost as many individual patients, and it is unclear whether an increase of the oral dosage might have provided similar effects. Nevertheless, the study is important because it proves that the better bioavailability of the s.c. administration is associated with better response rates.

In another recent trial on intensive *vs*. conventional treatment with MTX in early RA, the 2-year-Computer-Assisted-Management in Early RA study (CAMERA), remission was more often achieved in the former group, in which, however, there were also more adverse events (68). To compare the value of the two strategies, both beneficial effects and adverse effects are important to weigh. The aim of this study was to compare toxicity profiles between both MTX treatment strategies and to study possible associations between baseline characteristics with MTX withdrawal and liver toxicity during follow-up by using logistic regression analyses. Patients in the conventional treatment group attended outpatient clinic once every 3 months vs once per 4 weeks in the intensive treatment group. Both groups could increase their MTX dose to 30mg/week in case of insufficient response, and after s.c. administration of MTX, cyclosporine was added. All recorded adverse events were relatively mild and often reversible, but significantly more patients in the intensive treatment group *vs*. those in the conventional treatment group had MTX-related adverse events. The authors concluded that the previously observed clinical efficacy of an intensive treatment strategy seems to outweigh the observed toxicity profiles.

Multiple regression analyses showed that higher body mass index (BMI) was significantly associated with study withdrawal for MTX-related adverse events. There was also a trend towards decreased creatinine clearance being associated with MTX withdrawal. Liver toxicity during follow-up was predicted by higher serum liver enzyme levels at baseline.

A possible conclusion from these two studies is that in very active patients with a high risk of structural damage a high dosage, fast escalation and parenteral use of MTX appears preferable, while the oral route with a lower dosage and slower escalation steps seems easier and is acceptable for most RA patients in terms of tolerability.

Use of methotrexate in daily practice

In daily practice, the handling of MTX is based on the response to the initial dosage and administration, and to the comedication such as corticosteroids which are usually necessary to have some immediate efficacy and suppression of disease activity.

When the intake is tolerated for the first 4-8 weeks there are several scenarios possible when the patient comes to the rheumatologist for the next visit:

1. MTX is tolerated well and seems to be effective;
2. MTX is effective but not tolerated (well);
3. MTX is not effective but tolerated (well);
4. MTX is neither effective nor tolerated well.

There are several points to consider:

1. the initial dosage was too high (too low);
2. the route of administration was not the best option for this patient;
3. the serum folate level was too low (folate deficiency);
4. the renal function is or has become compromised;
5. the comedication may lead to altered serum levels of MTX.

Therefore, there are different possible consequences.

1. increase (reduce) the dosage;
2. split the dose;
3. change the way of administration (oral to s.c./i.m. or vice versa);
4. add (more) folic acid;
5. change comedication;
6. increase fluid intake;
7. wait and see.

Taken together, MTX remains to have a central role in the treatment of RA. The handling of MTX therapy can be rather complicated in some patients. Several aspects related to efficacy and toxicity need to be addressed for monitoring. An individual approach based on the activity and severity of the disease, and the risk profile of the patient, related to both, efficacy and safety, is needed for an optimal management. More studies are needed to optimise the care of patients with RA.

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