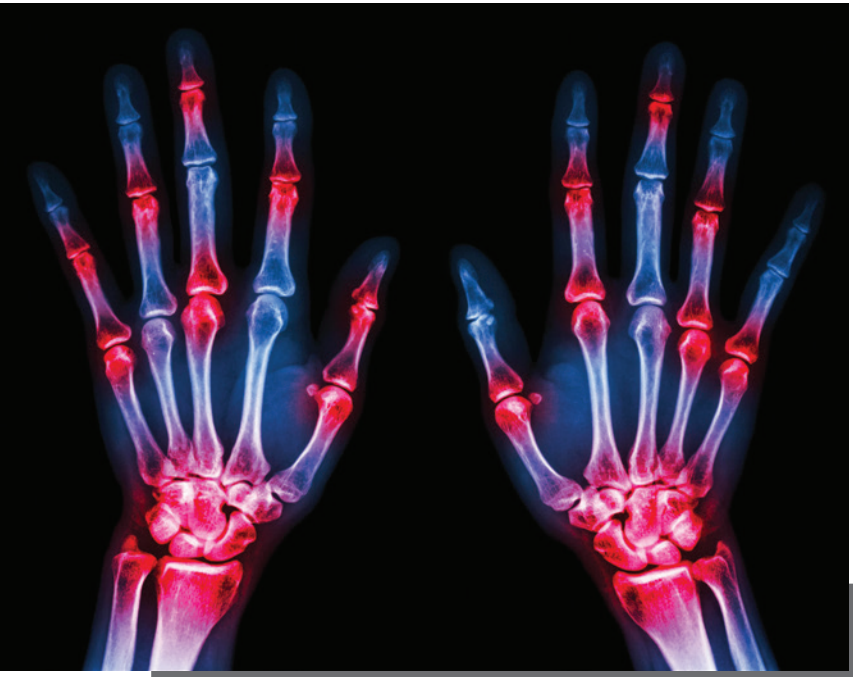

Optimising methotrexate treatment for rheumatoid arthritis

A practical guide for healthcare professionals

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Prologue

Methotrexate (MTX) is a remarkable drug that has a major place in the management of rheumatoid arthritis (RA) (and other indications) at every stage of the evolution of the condition. It is unusual among disease-modifying anti-rheumatic drugs (DMARDs), not only for its very favourable benefit:risk ratio and cost-effectiveness, but also because it can be administered orally or parenterally and has an unusually large dose range, which allows it to be titrated to clinical response according to the needs of an individual patient. Furthermore, MTX is used as an 'anchor drug' to which other synthetic or biologic DMARDs can be added with beneficial efficacy gains. As with any drug, MTX can be associated with adverse events, including tolerability problems. Many of the associated adverse events can be mitigated through careful monitoring, good patient education and appropriate management. The importance of MTX in the treatment of RA is acknowledged in international recommendations for the management of this condition.

However, although many recommendations emphasise the place of MTX in the treatment paradigm for both early and established disease, we have found there to be less readily available information with respect to how to get the best out of MTX and tailor its use to the unique needs of the individual. The authors of this booklet are all busy practising rheumatologists working across diverse clinical and geographical environments. They have expert knowledge of the most recent advances in rheumatology, as well as an abundance of experience in the art and science of using MTX to manage people living with RA.

It goes without saying that MTX should be used with reference to the Summary of Product Characteristics or Prescribing Information for a practitioner's country, and also to national and international guidelines; the information in this guide is not intended to replace these, but rather to supplement them.

In compiling this booklet, the authors have drawn upon the available evidence in peer-reviewed literature and international guidelines, as well as their own wide-ranging experience. Our goal has been to produce a practical, evidence-based guide to using MTX in adults with diagnosed RA or with early inflammatory arthritis that is suspected to be RA. Where the evidence base is not adequately informative, any opinions expressed are those of the authors.

We hope that the reader will find this work both helpful and informative, and that the patients under your care will derive the maximum possible benefit from prescribed MTX.

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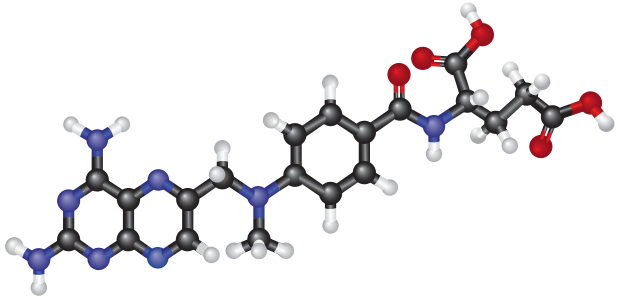
Introduction to MTX and its clinical use

What is MTX?

Methotrexate (MTX, 4-amino-10-methylfolic acid) is a folate analogue metabolic inhibitor, or antifolate agent, that has been licensed for the treatment of rheumatoid arthritis since 1988 (Figure 1).[1] It is also approved for use in severe Crohn's disease, severe psoriasis, and a variety of solid and blood cancers.[2] For rheumatoid arthritis MTX is available as an oral formulation of 2.5 mg, 5 mg or 10 mg tablets, and as a solution for subcutaneous injection marketed in prefilled syringes or auto-injectors.

Figure 1. The chemical structure of methotrexate[3,4]



MTX is classed as a conventional synthetic (cs) disease-modifying anti-rheumatic drug (DMARD) because it is a synthesised chemical compound that inhibits the disease processes that cause rheumatoid arthritis; it can thereby improve long-term functional outcomes, as distinct from providing only symptomatic relief.[5-7] Although MTX was originally developed to deprive proliferating cells of the folic acid they require for replication, it did not arise from the kind of advanced drug discovery programmes that are now used to design and engineer molecules, and this is why MTX is referred to as a 'conventional' DMARD.[7,8] Originally, all DMARDs were synthetic drugs, but now that there are additional types of molecular entities a uniform classification has been proposed to distinguish them (Table 1).[7]

Table 1. Categorisation of drugs for the treatment of rheumatoid arthritis[7]

Category	Abbreviation	Meaning	Examples
Conventional synthetic DMARD	csDMARD	A chemically synthesised DMARD developed using traditional, empiric methods	MTX, sulfasalazine, leflunomide, hydroxy-chloroquine
Targeted synthetic DMARD	tsDMARD	A chemically synthesised DMARD specifically developed to target a particular molecular structure	tofacitinib, baricitinib, upadacitinib, filgotinib
Biological and biosimilar DMARDs	bDMARD	A DMARD that is made by or derived from a biological source. bDMARDs are antibodies, modified antibodies or proteins that are fused to part of an antibody molecule. Known as the originator or reference DMARD when there is subsequent development of a biosimilar molecule	adalimumab, certolizumab, etanercept, golimumab, infliximab, rituximab, abatacept, tocilizumab, sarilumab, anakinra

DMARD: disease-modifying anti-rheumatic drug; MTX: methotrexate

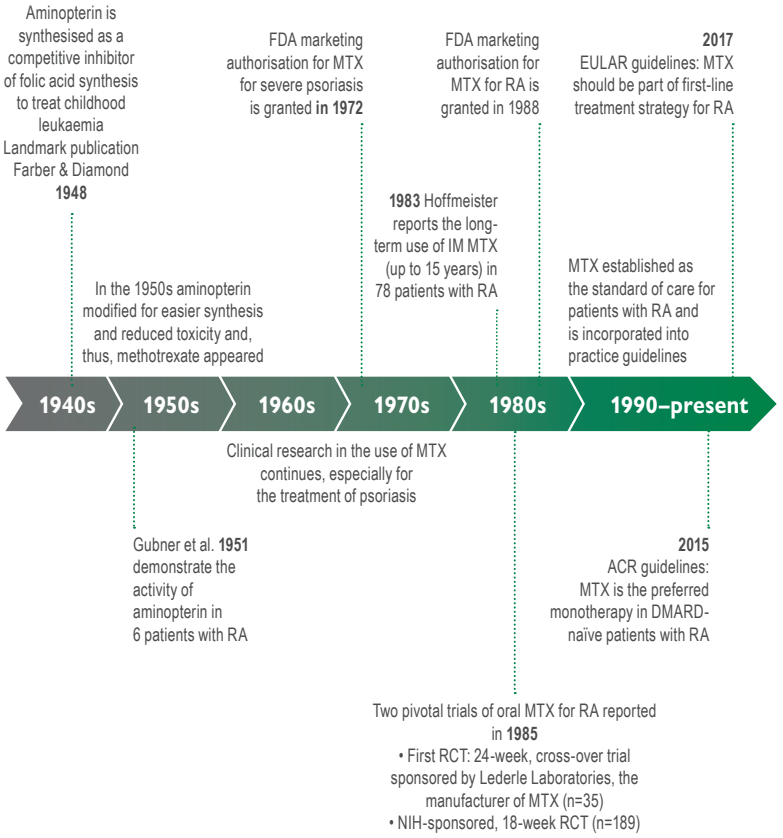
What is the history of MTX?

The clinical origins of MTX lie in the development of a treatment for leukaemia.[5] In the 1940s, it was observed that liver extracts believed to contain folic acid caused tumour regression when injected into tumour-carrying mice. Subsequently, patients with advanced cancer were administered synthetic folic acid with disastrous consequences – tumour growth was greatly accelerated. In fact, the active component of the liver preparation had been an antagonist of folic acid. Sidney Farber subsequently synthesised competitive inhibitors of folic acid, which he successfully trialled in children with leukaemia, as reported in 1948,[9] and so aminopterin, the forerunner of MTX, became one of the first chemotherapies for cancer.

Low-dose MTX for rheumatoid arthritis behaves quite differently from high-dose MTX used to treat cancer – the toxicity profile and primary mechanism of action are different.[10]

While MTX continues to be used for the treatment of cancer at high doses (grams), low doses (milligrams) were developed for anti-inflammatory conditions, initially for psoriasis and later for rheumatoid arthritis.[5] In the 1980s, MTX started to transform the prospects for patients with rheumatoid arthritis. In 1991, the disease-modifying properties that classify it as a DMARD were demonstrated when it was shown to slow the radiological progression of joint pathology.[11] The history of MTX as an approved drug for rheumatoid arthritis now spans more than 30 years (Figure 2).

Figure 2. Milestones in the evolution of MTX treatment for rheumatoid arthritis[5,6,9,12-18]



ACR: American College of Rheumatology; DMARD: disease-modifying anti-rheumatic drug; EULAR: European League Against Rheumatism; FDA: Food and Drug Administration; IM: intramuscular; MTX: methotrexate; NIH: National Institutes of Health; RA: rheumatoid arthritis; RCT: randomised controlled trial

What role does MTX have in the management of rheumatoid arthritis?

"MTX holds a unique place in the management of rheumatoid arthritis, with a role at every stage of the evolution of this chronic condition."[19]

Over the course of 25 years, MTX became the standard of care for treating severe rheumatoid arthritis, and both European and American guidelines now recommend MTX monotherapy as first-line therapy for rheumatoid arthritis.[6,16,20] MTX has stood the test of time as a cornerstone of therapy, even in the face of new, highly effective pharmaceuticals, including the biological DMARDs (bDMARDs) and, more recently, targeted synthetic DMARDs (tsDMARDs). This is in part because the benefits of MTX span the spectrum of rheumatoid arthritis progression; it is used as monotherapy for newly diagnosed rheumatoid arthritis and later as an anchor drug in many combination regimens, partnering with both well-established and newer therapies.

MTX has a unique combination of attributes that make it a flexible option for different individuals.[19] Balancing toxicity and tolerability with efficacy can be a challenge for many drugs. This is made easier with MTX because it has a wide titratable dose range, which gives scope for the widely used 'step-up' approach, whereby a patient is started on a dose likely to have good tolerability and then escalated to higher doses according to therapeutic response.[19] MTX also has the versatility of oral and parenteral preparations, which offers patients a meaningful choice in how they take the drug. Moreover, it affords the option of switching from the oral route to a parenteral route in order to improve bioavailability and reduce gastrointestinal adverse effects, should this be necessary for some patients.[19] Individualising dosage regimens is facilitated by the range of tablet strengths and the availability of prefilled syringes and auto-injectors, with various doses per injection.[19]

As well as its suitability for a 'step-up' approach to dosing, MTX is a key combination partner with other csDMARDs and bDMARDs as part of 'step-up' strategy that introduces new drugs in progressive lines of therapy when responses are, or become, inadequate. It is said to be 'clinically efficient' because it is an effective monotherapy in many patients for a substantial period of time, and can therefore help avoid patients being exposed to the potentially higher risks of combination therapies for longer than necessary. MTX is relatively inexpensive compared with bDMARDs, and this clinical effectiveness translates into a cost-effectiveness that contributes to its popularity.

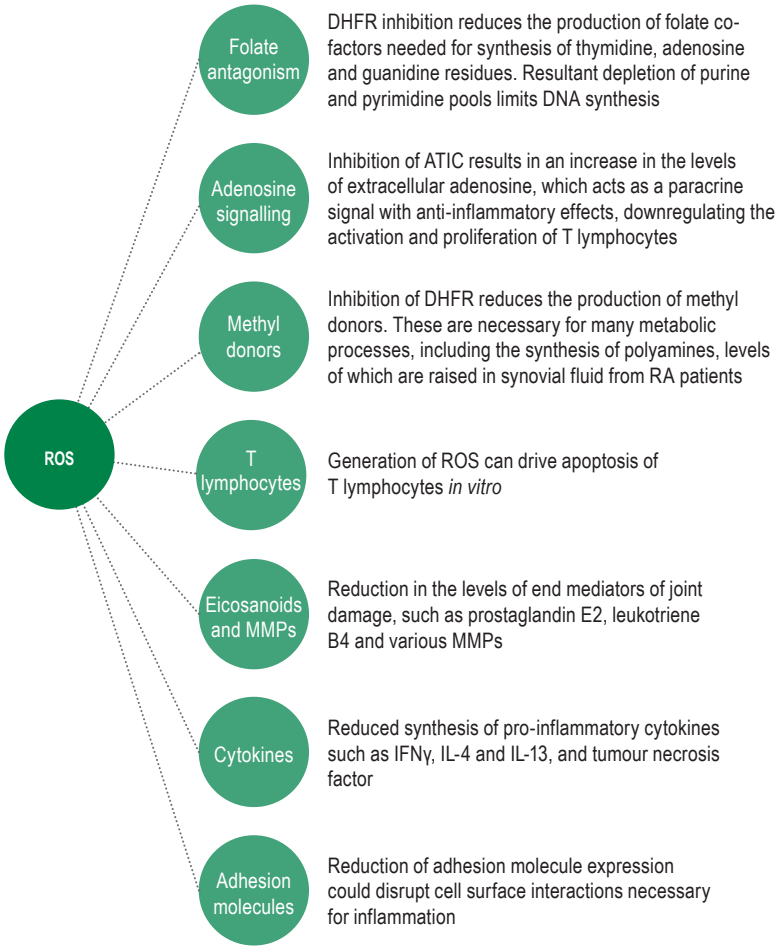
Fundamentally, MTX can be an effective DMARD for many patients. A Cochrane network meta-analysis estimated a 41% probability of an ACR50 response to MTX monotherapy;[21] in the TEMPO trial, ~20% of patients receiving MTX monotherapy achieved and maintained disease remission for at least 2 years.[20,22,23,29] It is thus a cost-effective option that offers convenient dosage regimens to optimise treatment for individuals.

How does MTX work?

MTX is a prodrug that is activated inside cells by the serial addition of glutamate residues, in the same way as other naturally occurring folates – this is called polyglutamation.[24] Polyglutamation helps to retain MTX within the cell and increases its inhibition of three main enzymes – dihydrofolate reductase (DHFR), thymidylate synthetase (TYMS), and 5-aminoimidazole-4-carboxamide ribonucleotide transformylase (ATIC). There are several

hypotheses for the mechanism of action of low-dose MTX in rheumatoid arthritis that are dependent on these or other undefined targets, but the exact mechanism has not been fully determined (Figure 3).

Figure 3. Potential mechanisms of action for low-dose MTX in rheumatoid arthritis[19,24]



ATIC: 5-aminoimidazle-4-carboxamide ribonucleotide transformylase; DHFR: dihydrofolate reductase; IFN: interferon; IL: interleukin; MMP: matrix metalloproteinase; RA: rheumatoid arthritis; ROS: reactive oxygen species

When high doses of MTX are used in cancer treatment, folate antagonism limits the purine and pyrimidine synthesis needed for cell division and leads to apoptosis; this explains both its cytotoxicity to proliferating malignant tumour cells and frequent adverse effects such as pancytopenia and mucositis. The profile of low-dose MTX used in rheumatoid arthritis is quite distinct, and clinical evidence does not support the same mechanism of action – concomitant folate supplementation can alleviate MTX-mediated adverse effects without impacting clinical efficacy.[24] At the low doses used to treat rheumatoid arthritis, MTX is an anti-inflammatory drug, and current evidence points most strongly to potentiation of adenosine signalling as its mechanism of action.[24]

What is the pharmacokinetic profile of MTX?

Key aspects of the pharmacokinetics of MTX are shown in Table 2. There are several practical implications of particular note.

Differences in pharmacokinetics between oral and subcutaneous MTX inform the dose and route of MTX administration for an individual patient. The bioavailability of oral MTX reaches a plateau at doses of 15 mg, suggesting that there may be limited benefit for many patients in titrating oral doses above this as a once weekly dose. When the total oral weekly MTX dose exceeds 15 mg, bioavailability can be improved by splitting the dose in a twice weekly regimen;[25] however, this is not widely done in practice because is it less straightforward for patients to remember such a dosing schedule. The higher and less variable bioavailability of subcutaneous MTX, combined with its linear dose-dependency, make it an attractive option for switching if up-titration of oral MTX fails to produce an adequate response.

Subcutaneous MTX is 31% more bioavailable than oral MTX for the same 20 mg dose.[26]

To increase drug exposure beyond that achieved with a 15 mg oral dose, it may be necessary to split the dose or switch to subcutaneous MTX.

The slow and gradual kinetics of MTX activation by polyglutamation can explain, at least in part, the long lag time between initiation of treatment and observable clinical benefit. A response is generally seen in the first 6-12 weeks, but it may be 6 months before the maximum effect is reached.[27] If the dose of MTX is changed, it may take another 6 months to reach a new steady state of active MTX, and this is an argument for rapid dose escalation.[27]

The active forms of MTX accumulate slowly in cells long after it has disappeared from the circulation. It can take ~28 weeks for active metabolites to reach 90% of maximum steady-state concentration.

This means that patients may need to take MTX for 6 months before experiencing its maximum benefits.

Approximately 90% of MTX is excreted by the kidneys. The potential for over-exposure to MTX should therefore be considered whenever there is impaired renal function, including physiologically reduced renal impairment in the elderly, post-operative renal dysfunction, and when concomitant medications may compete for active transport.[19,28] Rapid removal of MTX by dialysis is unlikely to be effective because polyglutamation retains the drug inside cells long after it has been cleared from the bloodstream.[29]

Be vigilant for any reduction in renal function, as it may lead to the accumulation of MTX.

Check if concomitant medications are likely to compete with MTX for excretion by the kidneys.

Table 2. The pharmacokinetics of oral and subcutaneous MTX[19,24]

	• Oral bioavailability: ~30–70%, with high interindividual variation but only modest intraindividual variation[30] • Systemic exposure plateaus at doses ≥15 mg/week[26]
	• Higher relative systemic bioavailability than oral MTX – 131% and 141% for doses of 20 mg and 25 mg, respectively[26] • Less variable exposure than with oral MTX • Linear, dose-dependent increase in bioavailability up to 25 mg[26] • Higher intracellular levels of long-chain polyglutamated MTX molecules compared with oral MTX
	• Oral MTX is absorbed by active transport from the small intestine • This mechanism limits bioavailability and is also a source of variability in exposure to MTX[31]
	• A small proportion of MTX from the gut undergoes first-pass metabolism in the liver, and ~10% of excretion is in bile[32]
	• Peak plasma concentrations after oral or subcutaneous administration are reached in ~1.5 hours[26] • ~50% circulating MTX is bound to plasma proteins[33] • Plasma half-life: median 4.5–10.0 hours[24] • MTX has a high tissue distribution, and is undetectable in serum by 24 hours after administration[8]
	• Primarily excreted by the kidneys through glomerular filtration and active tubular excretion

- Inside cells, MTX is activated by progressive polyglutamation i.e. the serial addition of up to 5 glutamate residues
- Estimated half-life of accumulation of glutamated MTX: median 8.3 weeks[27]
- Time for glutamated MTX to reach 90% of maximum steady-state concentration: median 27.5 weeks[27]
- Elimination half-life from cells: median 1.2–4.3 weeks[27]
- Longer-chain polyglutamates may be more clinically important; these take longer to appear and reach steady state than shorter-chain poly-glutamates[27]

- A median of 28 weeks is needed to achieve steady-state intracellular levels of MTX, which occurs when a balance is reached between activating polyglutamation and deglutamation
- Variability between patients in time to reach steady state depends mainly upon age, renal function and MTX dose[34]

MTX: methotrexate

What are the most important clinical challenges of using MTX?

The two main clinical challenges of managing patients with MTX are the long lag-time to a full response, and tolerability, especially with oral administration.

It may take up to 6 months to reach an optimal response to a given MTX dose, but current practice is to make a treatment adjustment after 3 months if the agreed disease activity target has not been attained. Crucially, although patients may not see the full effectiveness of MTX for many weeks after the initiation of MTX, they may still experience adverse effects. This is therefore a high-risk time for patients to prematurely discontinue MTX treatment. Clinicians should be alert to this, and take pre-emptive action to avoid having patients stop MTX treatment prematurely, and therefore miss the opportunity to gain the many health benefits of this drug. Engaging fully with patients is key. Patients need to be given clear and complete information on what to expect, and to be part of the decision-making process. They must also be motivated to take responsibility for complying with the treatment plan, in terms of both taking medication correctly and attending clinics to have blood tests as part of the monitoring requirements. Bridging corticosteroids may be used during this time to reduce inflammation and other symptoms of rheumatoid arthritis, thereby giving patients symptom respite and helping them to persist with MTX until its full effectiveness can be evaluated.[6]

Help patients to persist with MTX treatment for long enough to see its maximum benefits. Manage their expectations, and use bridging corticosteroids to reduce inflammation in the time preceding maximum MTX effect.

The risk of liver toxicity has always been a concern with MTX treatment. Regular monitoring of liver enzyme levels is an essential component of safety monitoring for patients, especially in the first 6 months of treatment.[16]
Approximately 50% of patients will have liver enzyme levels above the upper limit of normal during the first 3 years of MTX treatment.[35] Nevertheless, although frequent, elevations in liver enzymes levels are usually mild and transient. Direct, histologically confirmed hepatic toxicity is uncommon with MTX, even in patients with liver enzyme elevations more than 3 x the upper limit of normal.[36] More common in such patients are autoimmune hepatitis-like lesions associated with the underlying rheumatoid arthritis. The clinician needs to avoid unnecessary discontinuation of MTX because of small elevations in liver enzyme levels, and at the same time reduce other risks for liver injury, such as excessive alcohol consumption and the use of other potentially hepatotoxic drugs such as non-steroidal anti inflammatory drugs (NSAIDs) (refer to Table 5, page 62). The American College of Rheumatology (ACR) guidelines recommend against consuming alcohol while on MTX treatment.[37] In practice, however, clinicians may need to

take a more pragmatic approach based on the individual patient. If a patient has no risk factors for liver toxicity other than MTX treatment, many rheumatologists would allow modest alcohol consumption, preferably avoiding any alcohol on days when MTX is administered.[19]

15–20% of patients treated with MTX will experience minor, generally transient elevations in liver enzyme levels.[38] MTX-specific liver lesions are rare, even during long-term MTX treatment.[36]

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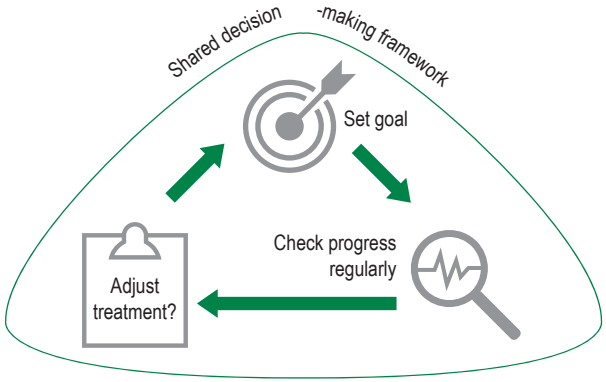
MTX as a first-line treatment: dosing and dose escalation

Does MTX treatment fit within a treat-to-target strategy for management of rheumatoid arthritis?

A treat-to-target approach to rheumatoid arthritis is fundamental to best practice whatever the drug therapy used, including MTX, and is embedded in current guidelines.[1-3] In practice, this approach incorporates five principles: the definition of a treatment target; regular monitoring of disease activity, using composite measures that include joint counts; adaptation of therapy if the treatment target is not met within a particular timeframe; consideration of the individual patient's clinical status; and shared decision-making with the patient.[4]



The recommendation to treat patients with a DMARD as soon as a diagnosis of rheumatoid arthritis has been made is now well established.[3] As a recommended first-line treatment, MTX should be initiated early and followed through within the framework of treat-to-target, which should guide dose escalation and/or intensification of treatment.

Treat-to-target is a treatment strategy that highlights the need for rigorous management of all patients as individuals. The initiation of MTX is not an exact science; the initial dose and subsequent dose adjustments demand clinical judgement with respect to a range of individual patient factors, such as age, gender, ethnicity, weight and renal function.[4]

What is meant by using MTX as an 'anchor' DMARD?

MTX has a long history in the treatment of rheumatoid arthritis, and even in the current era of bDMARDs and tsDMARDs it continues to be the recommended 'anchor' DMARD.[2,3,5] This means that it is used as a first-line treatment to which other DMARDs can be added if or when a combination regimen is required.

The ACR 2015 Guidelines make a clear recommendation for MTX monotherapy, rather than other DMARD monotherapies or DMARD combinations, in DMARD-naive patients.[2] Multinational guidelines on the use of MTX also favour initial MTX monotherapy over MTX in combination with other csDMARDs, based on the balance between efficacy and toxicity.[5] The 2019 European League Against Rheumatism (EULAR) Task Force recommendations do not preclude using MTX as part of a csDMARD combination from the outset, but they no longer explicitly present this as the most favoured option.[3,6]

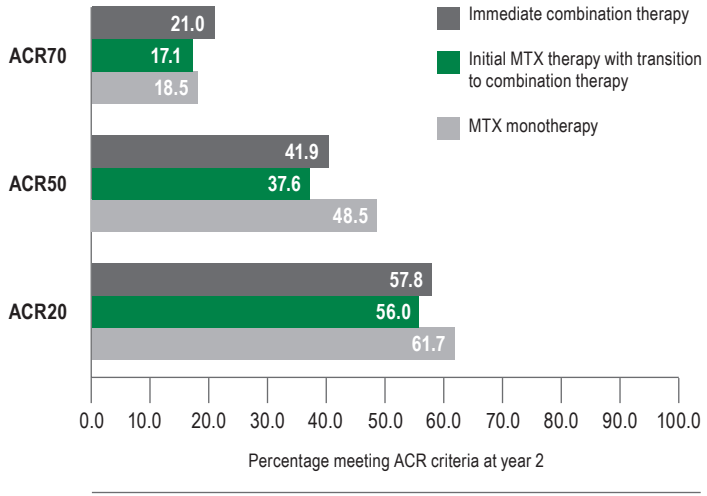
"MTX is recommended as first-line monotherapy because it is so clinically efficient. Much can be done to optimise MTX for the individual before resorting to additional drugs."

In the TEAR trial, 28% of patients with early, poor-prognosis rheumatoid arthritis achieved low disease activity (Disease Activity Score-28 with erythrocyte sedimentation rate [DAS28-ESR]) with MTX monotherapy at week 24, and did not need intensification of treatment with etanercept or hydroxychloroquine (HCQ) and sulfasalazine (SSZ).[7] Patients randomised to start with a combination of MTX and etanercept or a triple csDMARD regimen had better outcomes in the first 24 weeks; however, by weeks 48 to 102 there were no significant differences in efficacy between those patients and patients who started out with MTX monotherapy and stepped up to combination therapy (Figure 4).

The important point is that starting MTX as monotherapy with the option to step up to combination therapy later avoided 30% of patients receiving combination therapy unnecessarily, and did not compromise outcomes, including radiological progression, in those patients who did need to intensify treatment at week 24.[8]

The SWEFOT study also showed that nearly 30% of patients respond to MTX monotherapy[9], and data from real-life clinical practice support a strategy of MTX monotherapy with step up to combination as necessary.[10]

Figure 4. Effects of initial MTX monotherapy and MTX combination therapy in the TEAR trial[8]



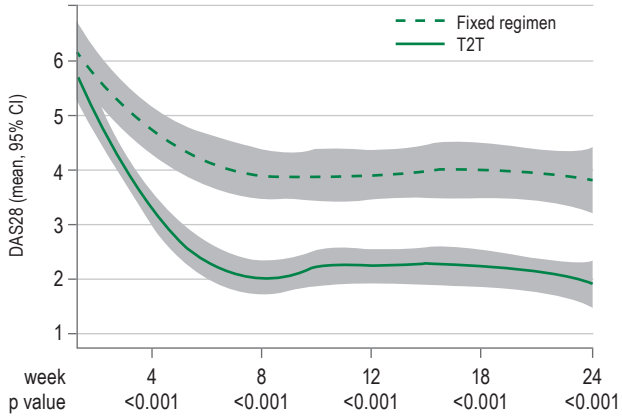
ACR: American College of Rheumatology; MTX: methotrexate

28% of patients have been reported to achieve low disease activity with MTX monotherapy.[7,8] Patients who do not respond initially and have a bDMARD added promptly are not disadvantaged compared with those who initiate MTX in combination with a bDMARD.[3,11]

The success of MTX monotherapy or a step-up MTX approach depends upon adaptive optimisation of MTX treatment. In the TEAR study, the dosage of MTX monotherapy was either raised at week 12 or lowered if, by that time, the patient had no active tender/painful or swollen joints.[7,8] Optimisation of MTX within a combination regimen may be equally important. A recent study compared outcomes in patients initiating certolizumab

pegol plus a fixed background regimen of csDMARDs and glucocorticoids, to patients initiating certolizumab pegol with csDMARD and glucocorticoid therapy that was progressively optimised in a defined treat-to-target strategy, e.g., by escalating MTX dose and adjusting the glucocorticoid dose.[12] The treat-to-target strategy with optimisation of csDMARDs was shown to be effective, and there was a trend towards superiority over the fixed csDMARD backbone (Figure 5).

Figure 5. Comparison of a fixed csDMARD and corticosteroid regimen with a csDMARD and corticosteroid regimen optimised in a treat-to-target strategy, both in combination with certolizumab pegol[12]
Reproduced with permission from reference 12, Mueller et al, 2019.



CI: confidence interval; csDMARD: conventional synthetic disease-modifying anti-rheumatic drug; DAS: Disease Activity Score; T2T: treat-to-target

What are the factors to consider when choosing the route of administration?

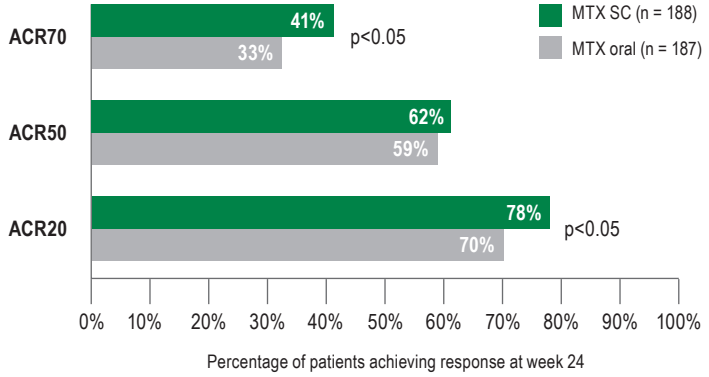
MTX can be administered orally, or by intramuscular or subcutaneous injection. Usually a decision is made between the oral or subcutaneous route, although national or hospital

guidelines may dictate which of these should be used initially. Individual patient preference will be explored within the shared decision-making process; research demonstrates that generally there is a preference for oral over parenteral drugs.[13,14]

Route of administration is a key driver of patients' treatment preferences, and most patients prefer oral treatments over injections.[13,15] Nevertheless, approximately one-third to half of patients in some studies populations prefer subcutaneous injections over oral treatment.[14,15]

In terms of clinical efficacy, there is growing evidence in favour of subcutaneous MTX. In a randomised controlled trial, patients initiated on 15 mg/week of subcutaneous MTX had better clinical outcomes than those starting with the same dose given orally (Figure 6), and there was no difference in tolerability.[16]

Figure 6. A comparison of responses to subcutaneous MTX with oral MTX[16]



ACR: American College of Rheumatology; MTX: methotrexate; SC: subcutaneous

In a large, prospective cohort study, subcutaneous MTX was associated with a lower rate of treatment failure and small but significant improvements in disease control (measured by DAS28) compared with oral MTX, but no difference in failure rate due to toxicity (Table 3).[17]

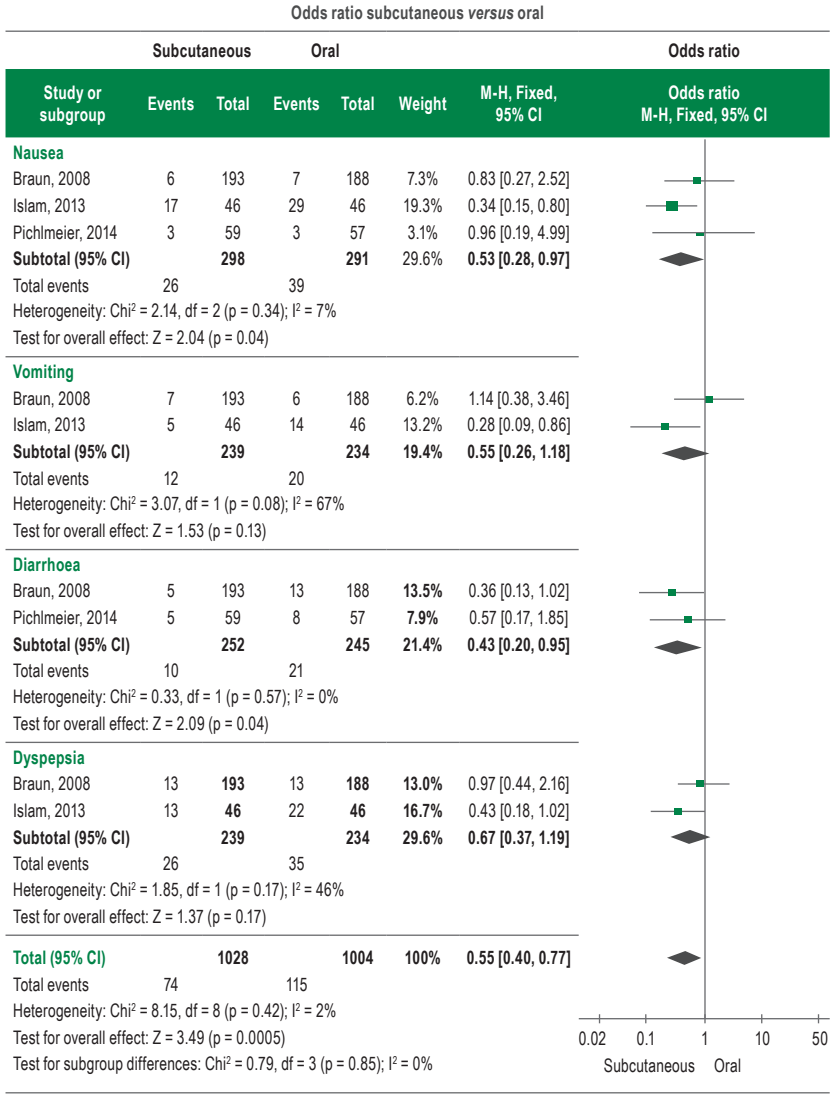
Table 3. Treatment failures with subcutaneous MTX compared with oral MTX in patients with early rheumatoid arthritis in the CATCH study[17]
Reproduced with permission from reference 17, Hazlewood et al, 2016.

Treatment failure by reason	SC MTX (n=249)	Oral MTX (n=417)	P value
Total treatment failures, % of patients	49	77	<0.001
Lack of efficacy only, % of patients	28	59	<0.001
Toxicity/tolerability, % of patients	3	2	0.63

MTX: methotrexate; SC: subcutaneous

In fact, there is evidence from a number of studies that subcutaneous MTX is associated with fewer and/or less severe gastrointestinal adverse effects.[18] A meta-analysis of seven studies showed that, in addition to better ACR20 and ACR70 outcomes, patients receiving subcutaneous MTX were less likely to have nausea or diarrhoea than those receiving oral MTX, although the risk of vomiting was not significantly different (Figure 7).[19]

Figure 7. A meta-analysis of gastrointestinal adverse effects associated with subcutaneous MTX compared with oral MTX[16,19-21]
Adapted with permission from reference 19, Li et al, 2016.

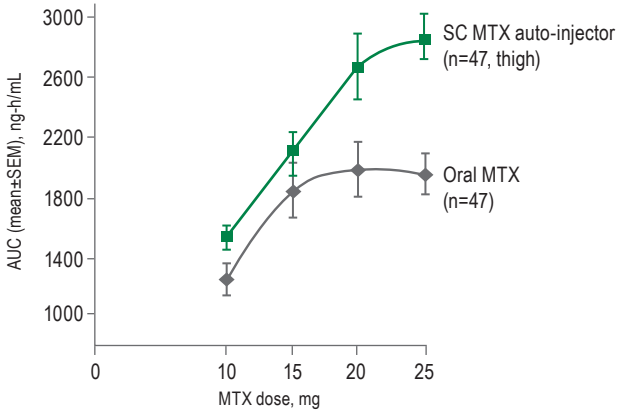


CI: confidence interval; M-H: Mantel-Haenszel; MTX: methotrexate

Pharmacological differences between oral and subcutaneous MTX may also inform the choice of administration route (Table 2). The bioavailability of oral MTX is limited by active uptake from the gut; once the dose reaches 15 mg/week there is little additional exposure at higher doses, shown as a plateauing of the dose-exposure curve (Figure 8).[22]

This suggests that there is limited benefit to administering oral MTX at doses greater than 15 mg/week. In contrast, linearly with dose between 10 and 20 mg. Furthermore, subcutaneous MTX has relatively higher bioavailability than oral MTX for doses ranging from 10 mg to 25 mg and the bioavailability is less variable.[19,22,23]

Figure 8. The impact of the route of administration and dose on exposure to MTX in patients with rheumatoid arthritis[22]
Reproduced with permission from reference 22, Schiff et al, 2014.



AUC: area under the concentration–time curve; MTX: methotrexate; SC: subcutaneous

Taking these considerations together, many clinicians prefer to start with oral MTX and keep open the option of switching to subcutaneous MTX in the event of an insufficient response after oral dose escalation.[5]

Subcutaneous MTX is more bioavailable than oral MTX, and is generally associated with better efficacy outcomes and fewer gastrointestinal adverse effects.

What should the starting dose of MTX be?

Multinational guidelines for MTX recommend initial oral doses of 10–15 mg/week.[5] In practice, starting doses range from 7.5 mg to 25 mg/week, and allowance must be made for individual patient factors including age, ethnicity, body weight and history of intolerance to other drugs.[4]

Recently, there has been a trend towards more aggressive initiation of oral MTX by using higher starting doses, based on the hypothesis that this might reduce the time to reach steady state for the longer-chain MTX poly-glutamates, believed to be more clinically important than shorter-chain MTX polyglutamates.[24,25] However, there are potential drawbacks to this approach. For example, higher doses of oral MTX potentially risk more gastrointestinal adverse effects[26] and discontinuations due to tolerability issues such as nausea. The wide range in oral bioavailability of MTX between patients[27] also suggests that a high starting dose of MTX risks over-treatment in some patients. Furthermore, in a meta-regression analysis of 31 studies, starting with a higher dose of MTX was not associated with better clinical outcomes.[24] If MTX is discontinued on the basis of poor tolerability and subsequently restarted, this should be at a previously tolerated dose.[4]

Generally, start with an MTX dose of 10–15 mg/week, using clinical judgement according to the individual situation, including factors such as age, body weight, comorbidity and ethnicity, etc.[4]

What is the best dose escalation strategy?

A core principle of treating to target is the progressive adaptation of therapy if treatment targets are not met within the predetermined timeframe. For MTX, this means dose optimisation by incrementally increasing the dose, up to the maximum tolerated dose if necessary, until a patient has achieved remission or at least low disease activity.

In a French observational national cohort, only ~25% of patients were receiving the optimal dose of MTX. Getting the optimal dose is critical to success – it can make remission four times more likely.[28]

An analysis of patients in the observational ESPOIR cohort defined optimal dosing of MTX as a starting dose of at least 10 mg/week during the first 3 months, with escalation to at least 20 mg/week at 6 months.[28] Patients dosed optimally were ~4 x more likely to achieve ACR-EULAR remission at 1 year (odds ratio 4.28) compared with those dosed non-optimally; results were similar in the second year.

In the C-EARLY trial, DMARD-naive patients were started with a regimen of MTX 10 mg/week plus placebo or certolizumab pegol.[29] The dose of MTX was increased by 5 mg every 2 weeks, if tolerated, up to a maximum of 25 mg/week.[8] In the MTX plus placebo group, 39.4% of patients achieved low disease activity at week 52, and 9.2% of patients withdrew due to adverse events. These results support a starting dose of MTX of at least 10 mg/week, with dose escalation as rapidly as can be tolerated.[4]

Regional guidelines differ in the details of the MTX dose-escalating strategies they recommend. However, dose escalation should be rapid, and typically the maximum recommended dose is 25 mg/week. Multinational guidelines from 2009 specify an escalation of oral MTX of 5 mg every 2–4 weeks, up to 20–30 mg/week.[5]

Escalate MTX from a starting dose of 10–15 mg/week as quickly as possible according to individual clinical response.[4] Generally, aim to reach at least 20 mg/week after 6 months, but refer to local guidelines.[4]

The bioavailability of oral MTX at doses above 15 mg/week may be poor in some individuals.[22] Switching to subcutaneous delivery at doses of 15 mg/week or more may enhance achievable efficacy while improving gastrointestinal tolerability.

Is there any benefit in switching to subcutaneous MTX if oral MTX has not been effective or tolerated?

Multiple national guidelines support switching from oral to subcutaneous MTX if a patient has not achieved at least low disease activity after dose escalation to the maximum tolerated dose, or in cases of poor compliance.[30-32]

Although most of the data are retrospective, a variety of studies have demonstrated the effectiveness of oral to subcutaneous MTX switches made for reasons of inefficacy or intolerance (Table 4).[18,23] In one of the largest of these studies – the MENTOR study of 196 patients with rheumatoid arthritis – 51% of patients made this switch for reasons of inefficacy and 44% because of adverse events.[33]

The subsequent persistence rates for subcutaneous MTX were 83%, 75% and 47% at 1, 2 and 5 years post-switch. On the basis of the 2-year cohort data, only 13.7% of patients switching from oral MTX due to inefficacy also experienced treatment failure on subcutaneous MTX, and bDMARDs were only added in 11%. Of those patients who did not tolerate oral MTX, 22.2% discontinued subcutaneous MTX due to adverse events. In a randomised controlled trial that demonstrated better outcomes with initiating MTX orally rather than subcutaneously, patients who did not respond to oral MTX were switched to the same dose of subcutaneous MTX, and 30% achieved an ACR20 response.[16]

Table 4. Outcomes after switching from oral to subcutaneous MTX due to lack of effectiveness or toxicity/tolerability issues[23]
Reproduced with permission from reference 23, Bianchi et al, 2016.

Study	Outcome measure	Outcome after switching from oral to SC MTX	Number of months post-switch at which outcome was measured
Braun et al. 2008[16]	ACR20 in non-responders to oral MTX, % of patients	30	2
CAMERA study[34]	Mean reduction in DAS28 score from time of switch	0.3 0.5	1 4
	Response to SC MTX[a], % of patients	63	1
Mainman et al. 2010[35]	DAS reduction of ≥1.2 points, % of patients	74	6
	DAS score <3.2, % of patients	29	6
MENTOR study[33]	Continuation rate, % of patients	83 75 47	12 24 60
	Additional biologic therapy, % of patients	5.2 8.5	12 24

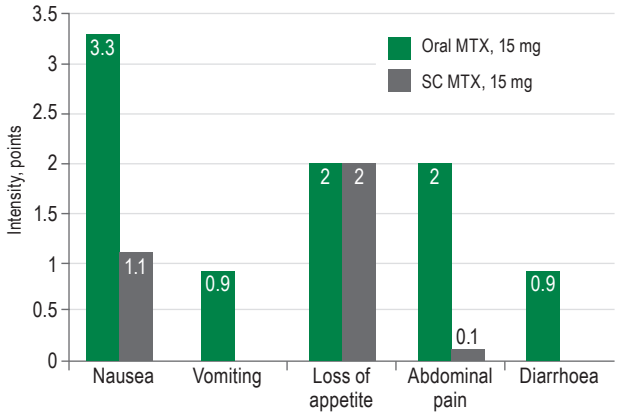
[a]Defined as an equal or better change in DAS28 1 month post-switch compared with the mean monthly DAS28 change during the 3 months prior to switch
ACR: American College of Rheumatology; DAS: Disease Activity Score; MTX: methotrexate; SC: subcutaneous

Switching to subcutaneous MTX can help patients to achieve higher circulating levels of MTX and at least delay the need for therapeutic intensification, especially the initiation of a bDMARD.[35-37] In a retrospective population-based study in the UK, 76% of patients who had switched from oral to subcutaneous MTX would have qualified clinically for anti-tumour necrosis factor (TNF) therapy and yet, 6 months after switching, 74% of patients responded sufficiently to avoid the need for bDMARD therapy.[35] The potential cost saving of switching to subcutaneous MTX rather than introducing a bDMARD has been demonstrated by analyses in both the UK and the USA.[36,38]

In an analysis of more than 35,500 patients in a US claims database who started oral MTX, switching to subcutaneous MTX delayed the initiation of biologic therapy by 706 days on average.[38] Total costs per patient were 3–4 x higher in patients who added or switched to a biologic compared with those who continued on oral or subcutaneous MTX.[38]

Switching from oral MTX to subcutaneous MTX may also reduce gastrointestinal adverse effects. In a survey of patients switching from oral MTX to the same subcutaneous dose due to gastrointestinal adverse effects, these effects were less intense after the switch; indeed, the proportion of patients reporting vomiting and diarrhoea fell to zero (Figure 9).[39]

Figure 9. The intensity of gastrointestinal adverse effects in patients switching from oral to subcutaneous MTX (15 mg weekly)[39]
Reproduced with permission from reference 39, Rutkowska-Sak et al, 2009.



MTX: methotrexate; SC: subcutaneous
Intensity was rated as 0, 2 or 4, corresponding to no symptoms, moderate/weak/slight symptoms, or strong/severe symptoms, respectively.

If patients do not respond adequately to oral MTX or have toxicity/tolerability issues, switching to subcutaneous MTX could have a number of benefits:
- *A better chance of achieving higher doses*
- *A better chance of delaying the need for a bDMARD*
- *Reduced gastrointestinal adverse effects*

How is the lag time to the maximum clinical benefit of MTX managed?

Whatever treatment regimen is used when initiating MTX, it may take up to 6 months for the full benefits to become apparent. Treatment response should be assessed at 3 months, and if there has not been a clinical improvement of at least 50%, adjustment of the treatment should be considered.[3]

The recommendation to use short-term systemic glucocorticoids to bridge the gap between the initiation of a csDMARD and the attainment of maximum effect has strengthened over time. There is growing evidence that a csDMARD plus glucocorticoid is not inferior to csDMARD combinations or bDMARDs plus MTX.[3] For example, in the CareRA trial, MTX with a moderate step-down dose of prednisolone had a favourable safety profile, and was as effective in inducing remission at 16 weeks as MTX combined with SSZ or leflunomide and moderate or high step-down doses of prednisolone.[40]

Bridging glucocorticoids should be gradually reduced and stopped within 3 months, and only exceptionally by 6 months.[3] Intra-articular glucocorticoids may be considered for a residually inflamed or reactivated joint.

Use systemic glucocorticoids to bridge the period between starting MTX and achieving maximum effect, but taper these as 'rapidly as clinically feasible'.[3]

Does MTX have any ancillary benefits in patients with rheumatoid arthritis?

MTX has been associated with reductions in all-cause mortality in patients with rheumatoid arthritis, probably mediated by its anti-inflammatory properties. In a large US cohort study, MTX was associated with a 70% reduction in all-cause mortality risk; this was observed only after more than a year of MTX treatment, but was independent of pain and disability measures of rheumatoid arthritis activity.[41] In another cohort, the survival benefit of MTX was greater with respect to cardiovascular deaths than non-cardiovascular deaths – 70% vs 40% reduction in mortality risk, respectively.[42] Patients with elderly-onset rheumatoid

arthritis can have a high risk for cardiovascular events due to comorbidities such as hypertension, diabetes and coronary artery disease.[43] In such patients, recent continuous MTX use has been associated with a 20% decrease in cardiovascular events.[43]

There is emerging evidence that the achievement of good disease control early in the natural history of rheumatoid arthritis may help prevent certain pulmonary comorbidities such as interstitial lung disease, as observed in two large, prospective, multicentre inception cohort studies conducted in the UK – the ERAS and ERAN cohorts.[44] This is an important observation, because interstitial lung disease is a potentially serious complication associated with poorly controlled, long-standing rheumatoid arthritis.[45] MTX has been implicated in an increased risk of lung disease in patients with rheumatoid arthritis,[46,47] but these associations may have been related to inadequately treated disease rather than to MTX itself.

In prospective inception cohort studies of patients with early rheumatoid arthritis, MTX exposure was associated with a significantly reduced risk of incident interstitial lung disease – an odds ratio of 0.48. In time-to-event analysis, there was a significantly longer time to diagnosis of the condition – an odds ratio of 0.41.[44]

There is some evidence linking MTX with a reduced risk for the development of dementia, although this association remains controversial. In a retrospective population-based study in the UK, MTX use appeared to halve the risk of dementia in patients with rheumatoid arthritis, with other csDMARDs reducing the risk to lesser extents.[48]

Dementia is associated with both systemic and localised inflammation,[49] and any effect of MTX might be hypothesised to derive from its anti-inflammatory properties.

Rheumatoid arthritis is one of the components of Felty's syndrome; despite the presence of neutropenia, which characterises the disorder, MTX is the first-line treatment for this condition.[50,51]

Good practice points

Start MTX treatment early – as soon as rheumatoid arthritis has been diagnosed
Treat to target
Start with MTX monotherapy and introduce other DMARDs only if they become necessary for an individual patient
The suggested starting dose for MTX is 10–15 mg/week
Escalate the dose as quickly as tolerability allows, in line with a treat-to-target strategy
If escalation of oral MTX is needed above 15 mg/week, consider switching to subcutaneous MTX
Consider switching to subcutaneous MTX if a patient has intolerance to oral MTX
Allow up to 6 months for MTX to take full effect

DMARD: disease-modifying anti-rheumatic drug; MTX: methotrexate

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Using MTX in combination with other DMARDs

When should MTX be used in a treatment combination?

"MTX is a great combination partner with other csDMARDs and with bDMARDs.

When used concomitantly with bDMARDs, MTX reduces the immunogenicity of administered protein[1] and acts synergistically to enhance achievable efficacy."[2]

MTX is the established "anchor" drug for patients with rheumatoid arthritis, and forms the foundation of combination regimens.

If a patient responds inadequately to MTX, combination with another csDMARD can be considered in the absence of poor prognostic factors.[3] In the presence of poor prognostic factors, the recommendation is to add a bDMARD or tsDMARD.[3] The EULAR Task Force has stated that all bDMARDs have better efficacy when combined with MTX compared with being used as monotherapy.[3] It is recommended that when bDMARDs and tsDMARDS are introduced to the treatment regimen, this should be as an add on to csDMARDs.[3] For patients with poor prognostic factors and severe rheumatoid arthritis, combination therapy may be needed from the outset in order to prevent irreversible functional impairment of the joints.[4]

Despite this guidance, MTX is still frequently stopped when bDMARDs or tsDMARDS are introduced.[4] In the USA, there has been a significant drop over time in the proportion of patients continuing with MTX therapy when a bDMARD is introduced: 74.1% in 2009 and only 45.4% in 2012.[5] These data suggest that MTX is being both underutilised and used sub-optimally, with potential detriment to long-term patient outcomes.

What drug combinations can be used with MTX in patients responding sub-optimally to MTX monotherapy?

MTX in combination with other csDMARDS

HCQ and SSZ are popular combination partners for MTX. HCQ increases overall pharmacokinetic exposure to MTX while reducing the maximum concentration of MTX and increasing the time to reach this.[6] Combining MTX and HCQ may be useful in patients who have had a response to MTX but without achieving the desired treatment target.[7]

If a patient has not responded adequately to MTX monotherapy and has no poor prognostic factors, triple therapy with MTX+HCQ+SSZ may have advantages over the initiation of bDMARDs.

In a Cochrane network meta-analysis, triple therapy with MTX+HCQ+SSZ had similar efficacy to MTX plus a bDMARD in patients with inadequate response to MTX monotherapy.[7]

MTX in combination with bDMARDs

bDMARDs should primarily be an add-on to a csDMARD, except in patients who cannot tolerate any csDMARD or have contraindications to them.[3] In general, the maximum benefits of bDMARDs are obtained in combination with a csDMARD such as MTX.[3]

Approximately two-thirds of patients will need to step up from MTX monotherapy to a more aggressive regimen.[8] Network meta-analysis has shown that switching patients who have experienced treatment failure with MTX (or other csDMARDs) to bDMARD monotherapy improves ACR50, function and rheumatoid arthritis remission rates compared with continued csDMARD treatment.[9] However, when response to MTX monotherapy is inadequate, the most relevant question may be whether a bDMARD or tsDMARD should be added to MTX or initiated as a replacement for MTX.

Randomised controlled trials in RA patients with treatment failure on MTX show that, when adding a bDMARD, whether it is an anti-cytokine, B-cell depleting agent, or co-stimulation blocker, combination therapy with MTX may be advantageous. For example, the JESMR study found that, in such patients, the numerical index of ACR response (ACR–N) at week 52 favoured an etanercept add-on strategy over switching to etanercept monotherapy.[10] Although radiographic progression at week 52 was not statistically different between the groups, the erosion score was negative in the add-on group at this time-point, and radiographic progression was reduced between weeks 24 and 52 compared with the switch group.[10]

Randomized controlled trials show that patients are more likely to respond to a combination of TNF inhibitor with MTX than to TNF inhibitor monotherapy.[10]

Potential explanations for the effectiveness of the combination of a bDMARD with MTX relate to their complementary mechanisms of action, pharmacokinetic interactions, and a reduction in the immunogenicity of the bDMARD.[4] In terms of their anti-inflammatory disease-modifying effects, TNF inhibitors and MTX together have a broader spectrum of efficacy than either drug alone.[11] TNF inhibitors primarily affect monocytes and dendritic cells, whereas MTX inhibits lymphocytes, so there is a synergistic therapeutic effect when the two are combined.[11]

As a combination partner with adalimumab, MTX appears to be effective at least partly because of its ability to lower the clearance of the bDMARD.[12] The efficacy of adalimumab can be limited by low serum concentrations. The CONCERTO trial showed that ascending doses of MTX, from 2.5 mg/week up to 10 mg/week, increased adalimumab serum concentrations, and this tracked with a significant trend for improving outcomes.[12] Adalimumab serum concentrations and clinical outcomes were similar for MTX doses of 10 and 20 mg/week. This important observation suggests that for patients on adalimumab who are intolerant of MTX at doses ≥ 20 mg/week, the benefits of combination therapy can be preserved by reducing the MTX dose to 10 mg/week.

After an initial response to a bDMARD, 30% of patients will subsequently experience treatment failure; the emergence of anti-drug antibodies is a major driver of such secondary failure.[13]

In an observational study of secondary failure with bDMARDs, anti-drug antibodies were found in 27.1% of infliximab-treated patients, 29% of adalimumab-treated patients and 0% of etanercept-treated patients.[14]

Concomitant MTX may prevent the formation of anti-drug antibodies to TNF inhibitors[1]. In this way, it may maintain the efficacy of the TNF inhibitor for longer, and potentially prevent immune complex-mediated adverse events.[15,16] The effect of MTX in reducing the immunogenicity of adalimumab and other biologic TNF inhibitors has been shown to be dose-dependent, supporting MTX dose optimisation when these drugs are used in combination.[16,17] Among csDMARDs, MTX has been demonstrated to be the most efficient drug in preventing the development of anti-drug antibodies to infliximab.[18]

The concomitant use of immunosuppressants, mainly MTX, reduces the proportion of patients with detectable anti-drug antibodies by ~41%.[1]

MTX in combination with tsDMARDs

The combination of MTX with the tsDMARD tofacitinib has demonstrated efficacy in patients with an inadequate response or intolerance to at least one DMARD, including MTX.[19] The ORAL Strategy phase IIIb/IV study, in patients who had an inadequate response to MTX, compared the efficacy of tofacitinib monotherapy, tofacitinib with concomitant MTX, and adalimumab with concomitant MTX.[20] In this study, the combination of tofacitinib and MTX was non-inferior to adalimumab plus MTX. However, tofacitinib as a monotherapy failed to meet the criteria for non-inferiority. Therefore, although tofacitinib monotherapy is a useful option for the minority of patients who are genuinely intolerant of MTX, better outcomes are

achieved when tofacitinib is used in combination with MTX. Similarly, in the RA-Begin trial of baricitinib in MTX-naive patients, while the improvement in symptoms and signs was similar for baricitinib as a monotherapy or in combination with MTX, the inhibition of structural damage was only significantly greater than with MTX monotherapy in the baricitinib + MTX arm.[21]

In light of these observations, the advice of the authors is to add a tsDMARD to MTX therapy at a well-tolerated dose of MTX. However, tsDMARDs can also be used as monotherapies in the minority of patients intolerant of MTX.

Should the dose of MTX be reduced when it is part of a combination regimen?

The evidence on MTX dose reduction when a bDMARD is added to the regimen has not established that this improves outcomes or reduces toxicity. In the TEMPO and COMET trials, patients were randomised to MTX monotherapy or combination therapy with MTX plus etanercept.[22] A *post hoc* analysis found that there were similar efficacy outcomes regardless of the MTX dose, suggesting that the dose of MTX can be lowered without compromising effectiveness.[22]

In the CONCERTO trial, patients had better clinical responses to a combination of adalimumab and MTX when the MTX dose was 10 or 20 mg/week compared with lower doses; however, this was a study in MTX-naive patients.[12] In patients with an inadequate response to MTX, the findings of the MUSICA study do not support routine dose reduction of MTX when adalimumab is added; lowering the MTX dose did not meet the non-inferiority criteria for clinical response compared with maintaining or increasing the MTX dose.[23]

However, finding the optimum MTX dose for an individual patient requires the achievable therapeutic response to be reviewed in the light of acceptable tolerability for that individual. Furthermore, whether MTX is used as a monotherapy or in combination with other csDMARDs or targeted therapies, MTX dose reductions may be required to manage adverse events. These include infections such as nasopharyngitis, which was associated with an ascending dose of MTX in the CONCERTO trial of adalimumab plus MTX.[12] Laboratory tests may also necessitate a MTX dose reduction, or even cessation; for example, in the event of persistent liver function test abnormalities or cytopenias.

Good practice points

Before adding or switching to another DMARD, check that the MTX treatment regimen has been optimised and that the patient is adherent
To get the maximum benefit from a bDMARD when there is an inadequate response to MTX monotherapy, add the bDMARD on to MTX rather than switch to bDMARD monotherapy
MTX helps to prevent the emergence of anti-drug antibodies to bDMARDs, and can thereby extend the durability of bDMARD treament
When a tsDMARD is initiated, this can be done as a combination with a well-tolerated dose of MTX

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Adverse effects associated with MTX

What are the potential toxicities and tolerability issues associated with MTX?

Mild tolerability issues with MTX are common in patients with rheumatoid arthritis: ~7–38% of patients discontinue MTX within the first year because of tolerability or toxicity.[1-3] The most common adverse effects of MTX are gastrointestinal, affecting 20–70% of patients in the first 1–2 years of treatment.[4] Specific tolerability issues include nausea, vomiting, diarrhoea, abdominal upset, anorexia, asthenia and fatigue.[4-6] Hair loss may occur in ~1–3% of people;[7] it usually develops gradually over time. As with any medication, patients and physicians should consider the benefits of treatment versus its adverse effects.

Mitigation strategies for poor tolerability of oral MTX:

- *Supplement with folic acid or folinic acid*
- *Switch from oral to subcutaneous MTX*
- *Split oral doses of MTX; however, the optimal regimen for dose splitting is unknown*

The overall benefit:risk ratio for MTX in rheumatoid arthritis is very good. However, it is important to appreciate common adverse effects that have quality-of-life implications, and mitigate these where possible to avoid premature discontinuation or poor adherence to MTX.

As with any drug, there is the potential for rare but serious adverse effects. Clinicians should know the signs and symptoms of these, relevant laboratory indicators, and the patient's risk factors, so that prompt diagnosis and treatment can be instituted (Table 5). Some adverse effects of MTX are exposure-dependent, and therefore the clinician should always be vigilant for any factors that may increase exposure, including reduced renal function and drug-drug interactions.

Table 5. The most frequent and serious adverse effects associated with MTX[8-10]

Adverse effects	Comments and mitigating actions
Most frequent adverse effects	
Gastrointestinal: nausea, vomiting, diarrhoea, abdominal upset, anorexia	• Supplement the patient with folate • Switch to subcutaneous MTX • Split oral doses of MTX
Hepatic: elevation in transaminases	Although increases in transaminase levels are common, symptomatic or severe hepatoxicity is uncommon • Perform regular liver function blood tests to monitor for sustained elevations outside the normal range • Supplement the patient with folate • Decrease or stop any concomitant NSAIDs (prescribed or self-administered) • Reduce/stop alcohol consumption • Treat obesity
Haematological: anaemia, neutropenia, thrombocytopenia	• Perform a complete blood count before initiating MTX
Skin: exanthema, erythema and pruritus	• Treat symptomatically and, depending on progress, ascertain the patient's perspective on the benefit of treatment versus the adverse effect before making a shared decision regarding ongoing treatment with MTX
General: headache, tiredness, drowsiness	• Discuss potential quality-of-life impacts with patients before initiating MTX. Ensure that the patient is adherent to adequate folic acid supplementation, and explain that some adverse effects of this nature may diminish with time. If this is not the case, ascertain the patient's perspective on the benefit of treatment versus the adverse effect before making a shared decision regarding ongoing treatment with MTX
Most serious adverse effects	
Hepatotoxicity: cirrhosis, fibrosis, fatty degeneration, decreased serum albumin, acute hepatitis, hepatic failure	The most clinically significant liver effects are rare or very rare • Check for risk factors prior to initiating MTX e.g. alcohol abuse, renal impairment, liver disease, impaired liver function, viral hepatitis; test for HIV in high-risk patients • Perform regular liver function blood tests • Reduce MTX dose if sustained elevations in ALT/AST are >1.5 x and <3 x ULN • Interrupt MTX if sustained elevations in ALT/AST are >3 x ULN • Discontinue MTX if ALT/AST levels remain >3 x ULN, and investigate • Be alert to the potential for renal dysfunction to develop e.g. post-operatively
Renal toxicity: clinically significant impairment in kidney function	• MTX is contra indicated if creatinine clearance is <30 ml/min • The dose should be reduced by 50% if creatinine clearance is 30–59 ml/min • Be alert to the potential for renal dysfunction to develop e.g. post-operatively

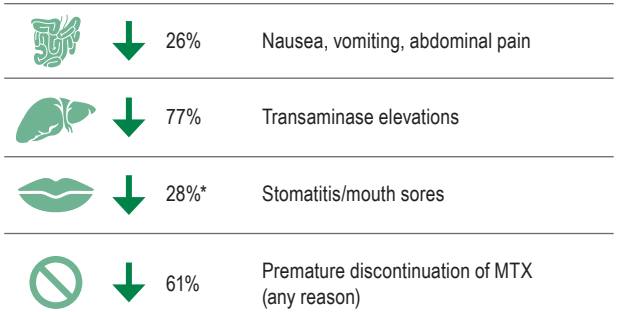
Adverse effects	Comments and mitigating actions
Most serious adverse effects	
Haematological: pancytopenia, bone marrow suppression	The incidence of clinically important pancytopenia is estimated to be <1% • Perform a complete blood count before initiating MTX, and monitor • Supplement the patient with folate • Do not use twice-daily trimethoprim-sulfamethoxazole to treat any infections
Lung: MTX-induced pneumonitis	MTX-induced pneumonitis is a hypersensitivity reaction that is potentially life-threatening • Be alert to acute symptoms including fever, non-productive cough and dyspnoea • Educate patients to contact their clinician if significant lung symptoms develop • Recognise and intervene early, including stopping MTX • Know the indicative patterns associated with pneumonitis in radiographs and CT scans
Nervous system: neurotoxicity	Serious adverse reactions are very rare
Cardiovascular: thromboembolic events	Rare
Immunological: anaphylactic shock	Rare
Skin: Stevens-Johnson syndrome	Very rare

ALT: alanine aminotransferase; AST: aspartate aminotransferase, CT: computerised tomography; HIV: human immunodeficiency virus; MTX: methotrexate; NSAID: non-steroidal anti-inflammatory drug; ULN: upper limit of normal

Is it beneficial to use supplementary folic acid with MTX?

Many patients with rheumatoid arthritis have folate deficiency, and those treated with MTX are even more likely to be folate deficient because of its antifolate activity.[9,11] Folate deficiency is associated with mouth sores, abdominal pain, elevation of liver enzymes and bone marrow depletion.[9] Multiple studies have demonstrated the effectiveness of folate supplementation in reducing the incidence of gastrointestinal tolerability issues and liver toxicity associated with MTX, and in reducing the number of patients discontinuing MTX treatment (Figure 10).[12,13]

Figure 10. Relative risk reductions in the adverse effects of MTX when patients receive folic acid or folinic acid supplements[12]



*Not statistically significant

MTX: methotrexate

In a systematic review, folic or folinic acid supplementation did not appear to have any significant effect on the efficacy of MTX in rheumatoid arthritis.[12] However, neither of them should be administered on the same day as MTX. In particular, folinic acid should be administered once weekly the day after MTX; doses of folinic acid >7.5 mg/week may negatively impact MTX efficacy.[9] Folic acid can be dosed from 5 mg/week up to 5 mg/day (except on the day of MTX administration).[9] Recent findings question the additional

benefits of high-dose compared with low-dose folic acid.[13,14] A systematic review concluded that there was no statistical difference between folate supplementation at ≥25 mg/week and ≤10 mg/week on either MTX toxicity or MTX efficacy.[13]

There is no reported evidence that folinic acid is significantly less effective than folic acid, but folic acid may be more cost-effective.[9]

Guidelines strongly recommend that patients with rheumatoid arthritis take at least 5 mg of folic acid per week with MTX therapy.[10]

Folic acid should not be administered on the same day as MTX, and taking it 2 days before MTX may improve its tolerability.[9]

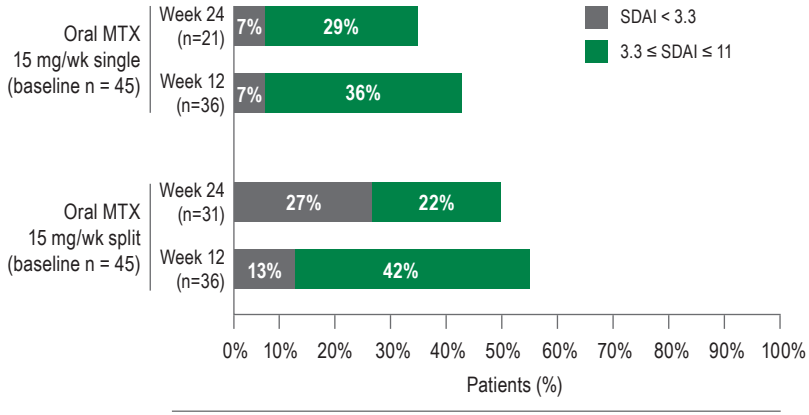
Is it helpful to reduce the dose of MTX to mitigate its adverse effects?

MTX dose correlates with the intensity of adverse effects, but its efficacy is also dose-related.[15-17] Thus, despite MTX having a wide titratable range, reducing the dose has the potential to impact negatively on efficacy,[17,18] and complete withdrawal of MTX is associated with disease flares. Dose tapering is a strategy to mitigate this risk of flares, but there are other possibilities: tapering/withdrawing MTX as part of a 'step-down' combination DMARD regimen; and tapering/withdrawing MTX when it is being co-prescribed with biologic agents.[19]

Clearly, there is a balance to be achieved between the adverse effects of MTX and maximising its effectiveness. The overall amount of MTX taken is not the only adjustment available – the dose can be split over the week.

Dividing 25–35 mg oral MTX into two doses has been shown to increase bioavailability by 28%.[20] In a small randomised study, a 15 mg or 22.5 mg oral dose of MTX was associated with better efficacy outcomes when it was split into 2 or 3 doses spread throughout the week rather than given as a single dose; the rate of adverse events was not affected (Figure 11).[21]

Figure 11. Efficacy outcomes with single or split doses of oral MTX assessed by the Simplified Disease Activity Index[21]



MTX: methotrexate; SDAI: Simplified Disease Activity Index

Before a decision is made to reduce the dose of MTX:

- *Consider switching from oral to subcutaneous MTX, which may reduce gastrointestinal adverse effects*
- *Splitting an oral dose is a potential option, but the optimal splitting regimen is unknown*
- *Use folate supplementation to reduce gastrointestinal adverse effects*
- *Check for drug-drug interactions and impaired renal function, which may increase exposure to MTX*
- *Check for concomitant use of non-steroidal anti-inflammatory drugs, which may both reduce renal function and cause elevations in liver enzymes*

What are the main drug interactions that need to be considered for MTX treatment?

The main drug-drug interactions for MTX are listed in Table 6.

Table 6. Key drug-drug interactions with MTX[9]

Interacting drug	Nature of interaction	Effect of interaction
Allopurinol, triamterene	Unknown	Increased MTX levels
Ciprofloxacin, cephalothin, penicillin, probenecid, sulfonamides	Decreased renal MTX clearance	
Diuretics, proton pump inhibitors	Decreased MTX excretion	
Probenecid	Increased MTX reabsorption by the kidney tubule	
Chloramphenicol, tetracyclines	Decreased intestinal absorption of MTX	Decreased MTX levels
Chloramphenicol, co-trimoxazole, pyrimethamine, sulfonamides, trimethoprim-sulfamethoxazole	Myelotoxicity	Increased risk of bone marrow suppression
Alcohol, leflunomide	Hepatotoxcity	Increased liver toxicity

MTX: methotrexate

Trimethoprim-sulfamethoxazole should not be used twice daily to treat infections in patients receiving MTX.
It may be used prophylactically three times per week for the prevention of Pneumocystis jirovecii.

Any drugs that affect renal function may increase MTX bioavailability, including NSAIDs, which have been shown to increase the risk of serious adverse events including renal failure and cytopenia.

Concomitant NSAID use has been reported to increase the incidence of serious adverse events by 40%.[22]

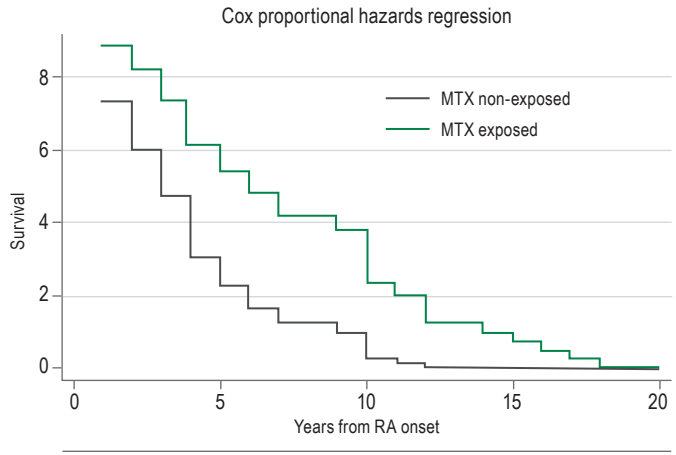
Exercise caution when prescribing NSAIDs for patients being treated with MTX.

Monitor self-medication with NSAIDs closely.

Does MTX cause interstitial lung disease?

Rheumatoid arthritis interstitial lung disease can affect ~10% of patients, and has potential to impact on mortality and morbidity.[23,24] MTX treatment has been implicated,[25] but a recent meta-analysis has failed to confirm an association between MTX treatment and rheumatoid arthritis interstitial lung disease.[26] Furthermore, a large multicentre rheumatoid arthritis cohort study that specifically addressed this question concluded that MTX was not associated with an increased risk of rheumatoid arthritis interstitial lung disease, and, in fact, may delay its onset (Figure 12).[27]

Figure 12. Time to onset of rheumatoid arthritis interstitial lung disease from first joint symptoms of rheumatoid arthritis[27]



Cox proportional time-to-event analysis showing time of onset of RA-ILD from first joint symptoms of RA in MTX-exposed (n=1578) and non-MTX-exposed (n=1114) groups.
ILD: interstitial lung disease; MTX: methotrexate; RA: rheumatoid arthritis

Interstitial lung disease is a common manifestation of rheumatoid arthritis. Recent data suggest that MTX is not associated with an increased risk of rheumatoid arthritis interstitial lung disease.[24,27-30]

Are there skin adverse events associated with MTX?

Patients with rheumatoid arthritis taking MTX have an increased incidence of non-melanoma skin cancer. In particular, higher cumulative MTX doses increase the incidence of basal cell carcinoma.[31] In the summer months or in countries with high sun exposure, it is advisable for patients with rheumatoid arthritis taking MTX to use sunblock (SPF ≥30) and wear a hat for sun protection.[32] MTX is not a photo-sensitising drug as such, but rather may produce a reaction called 'radiation recall'. Areas where patients have had sunburn in the past may react again after starting MTX.

Good practice points

Points to consider as part of best-practice care prior to initiation of MTX
Establish the diagnosis of rheumatoid arthritis and the need for treatment
Define the therapeutic aim
Engage the patient in shared decision making
Check for chronic kidney or liver diseases
Check for a diagnosis of active/chronic infection with herpes zoster, tuberculosis, hepatitis, HIV, relevant fungal infection
Check for a diagnosis of any immunodeficiency
Assess a baseline chest radiograph
Assess the patient's cardiovascular risk factors
Assess the status of neoplastic disease
Check for anaemia, leukopenia, or thrombocytopenia
Document vaccination status
Document concomitant drug therapy
Evaluate the mental status of the patient and their resilience and coping strategies
Discuss smoking habits and the benefits of stopping smoking
Evaluate alcohol consumption
Discuss matters relating to family planning and contraception, as appropriate

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MTX use in specific clinical scenarios

Can MTX be used in pregnant or breast-feeding women?

MTX is both an abortifacient and a teratogen, and is contraindicated during pregnancy.[1]

MTX is excreted in breast milk, and should not be used in breast-feeding women[1]

MTX treatment should be stopped in advance of a planned conception. Recommendations on the timing of this differ from 48 hours to 6 months, and therefore the clinician should consult national prescribing information and guidelines.[2] These may vary from one country to another. Any woman who has been treated with MTX within 3 months of conception should be prescribed supplementary folate at 5 mg/day throughout pregnancy.[3] If a woman has an unplanned pregnancy, MTX should be discontinued immediately.[3]

MTX is excreted in breast milk in low concentrations, and can accumulate in neonatal tissues. Therefore, it is contraindicated during breastfeeding. Both EULAR[4] and British Society for Rheumatology-British Health Professionals in Rheumatology (BSR-BHPR)[3] guidelines recommend that nursing mothers avoid MTX.

Can MTX be used in men whose partners are trying to conceive?

Previously, men were advised to stop taking MTX 3 months before attempting to conceive a child. This was not an evidence-based recommendation, and it is not supported by recent data. In a nationwide Danish study, 127 live births where the father was exposed to MTX were reported; there was no association between paternal MTX exposure in the 90 days before pregnancy and congenital malformations, stillbirths or preterm births.[5] Current British guidelines indicate that it is not necessary for men to stop taking MTX prior to fathering a child.[3]

Can patients be effectively vaccinated whilst on MTX treatment?

MTX significantly reduces the response to some vaccines because of its inhibition of the immune system. Patients with rheumatoid arthritis are more susceptible to infections than healthy individuals, and it is particularly important to protect them against influenza, pneumococcal and herpes zoster (shingles) infections.[2] The pneumococcal vaccine (PPSV-23) is recommended in immunosuppressed patients and should be repeated 5 years after the first vaccination.[6] Other inactivated vaccines (e.g. tetanus, diphtheria, pertussis, human papillomavirus and meningococcal vaccines) should be given according to the same indications and schedules as in the general adult population. Ideally, any vaccines an individual needs should be given prior to starting MTX treatment. If this is not possible, MTX can be temporarily interrupted – in the case of the seasonal influenza vaccine, stopping MTX for 2 weeks post-vaccination can help to mitigate a reduced response.[2,7]

In the case of live vaccines, MTX suppression of the immune system may put the patient at risk from infection by the vaccine strain. Live vaccines, such as yellow fever, measles/mumps/rubella, varicella, and oral typhoid vaccinations, are generally not recommended in patients being treated with MTX, although full consideration needs to be given to the circumstances of each individual case.[2]

Review the vaccination history for patients with rheumatoid arthritis. Check that patients are up to date on all routinely recommended vaccinations, as appropriate for their age and risk. For maximal protection, any inactivated (non-live) vaccines required should be given 2 weeks prior to initiating MTX treatment. If this is not possible, consider a temporary 2-week interruption in MTX treatment.[2]

Should MTX be discontinued before surgery?

Surgeons are sometimes concerned that use of csDMARDs around the time of surgical procedures may potentially increase the risk of infection and delay wound healing. However, the evidence does not support interrupting MTX for surgery. In a prospective trial of 388 rheumatoid arthritis patients undergoing surgery, the incidence of infections was significantly lower in patients randomised to continuing MTX than in those interrupting MTX treatment from 2 weeks before surgery to 2 weeks after (2% vs. 15%, $p<0.003$).[8] The risk of flares is another consideration; these occurred in 8% of patients interrupting MTX and in none of those continuing MTX.

Continue MTX treatment in patients undergoing surgery.[2,9]

Remain alert for any post-operative reduction in renal function, as this may increase both exposure to MTX and the risk of toxicity.

MTX and intercurrent infection

Patients with RA have a significantly increased risk of infection, particularly when the disease is active or when there are comorbidities present. However, MTX appears to be associated with minimal increased infection risk.

For patients with mild infections (e.g. the common cold, and infections not requiring antibiotics) it has been recommended that MTX is continued.[10] In patients with moderate infections (i.e. requiring antibiotic treatment), MTX should be withheld until the antibiotic course has been completed and the clinical symptoms have resolved. For severe bacterial infections (i.e. requiring hospital admission or intravenous antibiotics), MTX should be withheld until antibiotic treatment has been completed, inflammatory markers have returned to baseline levels and clinical symptoms have resolved.

In severe infection, particularly if there is renal impairment and/or dehydration, intravenous folinic acid rescue in the early stage of infection should also be considered.

During the 2020 SARS-CoV-2 pandemic, patients presenting with symptoms of Covid-19 have been advised to discontinue MTX until they are fully recovered, and to consult with their rheumatologist.

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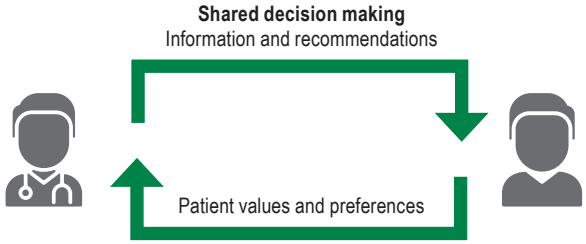
Shared decision making

What is shared decision making?



Shared decision making allows the clinician and their patient to individualise treatment together. It is a two-way process that is much more than the clinician providing the patient with information and asking them to make an informed decision. Balanced, evidence-based and contextualised information is key, but not sufficient. The patient needs to be able to consider and express their own values and preferences with all the facts at hand; equally, the clinician cannot formulate their recommendation for the patient on the basis of their clinical status alone – they need to understand their patient's perspective and motivation. Shared decision making encompasses the whole treatment strategy, including the goals of treatment and the management plan, as well as the choice of medication.[1]

Healthcare professionals and patients with rheumatoid arthritis worked together in one French study to determine what knowledge is essential for patients to manage their condition.[2] The knowledge areas that were most important, according to the number of items they encompassed as a percentage of all essential items across all knowledge areas, were pharmacological treatment (31.9%), disease knowledge (21.7%), adaptive skills such as relationships with healthcare professionals (17.4%), and non-pharmacological treatment such as joint protection and physical activity.

In a large global survey of clinicians and their patients with rheumatoid arthritis:[3]

- *61% of patients felt uncomfortable raising their concerns or fears with their clinician*
- *52% of patients believed that improved discussion would optimise the management of their rheumatoid arthritis*
- *88% of clinicians agreed that patients were more satisfied with their treatment experience if they were involved in decision making*

Can shared decision making work with a treat-to-target approach?

Patients with rheumatoid arthritis have a range of beliefs and attitudes towards potential treatments[4] that may sometimes negatively influence the patient's expectations of a treat-to-target approach. Indeed, data from the TRACTION trial in the USA showed that patient preference was a barrier to implementing a treat-to-target strategy in 37% of those visits where treatment was not adjusted despite failure to achieve a predetermined treatment target.[5] Patients may resist changes to their treatment based purely on disease activity. A survey in The Netherlands found that the five most important factors to patients with respect to a decision to escalate treatment were level of current physical functioning, motivation to get better, trust in their rheumatologist, satisfaction with their current DMARD, and current number of painful joints.[6]

Situational awareness modelling, however, has demonstrated that a collaborative treat-to-target strategy is feasible. Disease activity, in terms of current and recent pain, physical functioning and global disability, was important in the patient's assessment of the discrepancy between their current disease status and the desired status.[7] Beliefs about the effectiveness of treatment and the ability of the patient to control the disease were significant, but did not nullify considerations of disease activity; the single most important factor for the patient in assessing their progress was current pain. Clinicians assess disease activity using composite scores, and make predictions based on their knowledge and experience. Patients evaluate individual aspects of disease activity, and interpret these in the context of their own beliefs. Understanding both the commonalities and potentially complementary differences in approach should help to implement a workable treat-to-target strategy.

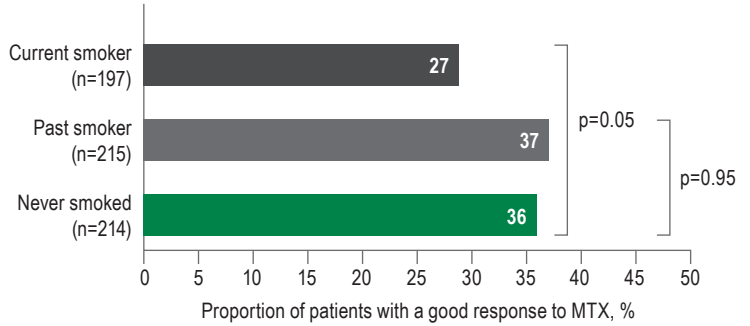
"Shared decision making requires listening carefully to the patient's own treatment goals, and explaining the best means to achieve what is realistically possible, while optimising overall outcomes both for the short and long term. The treatment strategy has to involve a benefit:risk ratio of treatment that is acceptable from the patient's perspective."

How can patients be helped to set themselves up for successful treatment with MTX?

There are some risk factors for a poor response to MTX that are said to be 'modifiable' and that patients can address themselves, with professional help in some circumstances.

Stopping smoking should be a priority. Smoking can negatively affect the pharmacokinetics and pharmacodynamic properties of MTX,[8] and predicts a poor response to MTX.[8-11] All patients should be encouraged to stop smoking, as past smokers respond as well to MTX monotherapy as those who have never smoked (Figure 13).[12]

Figure 13. Response to MTX monotherapy according to smoking status[12]



A good response was assessed using EULAR criteria at the 3-month visit.
EULAR: European League Against Rheumatism; MTX: methotrexate

The American College of Rheumatology advises against alcohol consumption during MTX treatment because of its potential to increase the risk of MTX hepatotoxicity.[13] The evidence for this association has been mixed,[14] but recent data provide more clarity. An analysis of the UK's national Clinical Practice Research Datalink showed that excessive alcohol consumption, defined as >21 units per week, was linked to an increased risk of transaminitis in patients with rheumatoid arthritis starting MTX therapy.[15] Weekly alcohol consumption of <14 units did not appear to increase the risk of hepatotoxicity;[15] therefore, modest intakes may be acceptable for most patients if hepatic enzyme levels remain within normal limits.[16]

Evidence from real-life clinical practice shows that anxiety is associated with non-response to MTX.[17] Honest and open discussion as part of shared decision-making gives the clinician the opportunity to allay any unfounded fears; communicating positive but realistic expectations may help reduce anxiety and improve outcomes.[16] Educating patients on what they can expect from MTX treatment, in terms of the likely magnitude of benefit, speed of onset and mitigation of potential toxicities, may also help them adhere to treatment, which will increase the likelihood of success.

"Many patients find information provided on package inserts to be highly alarming, and anxiety can be exacerbated by their own internet searches. It is essential that a patient can discuss the likely benefits and risks of a drug with their physician in an atmosphere of honesty and trust. Working together, a treatment regimen can be established and refined to give the best possible outcomes, while mitigating risks."

What are the benefits of shared decision making with patients?

The potential benefits of shared decision making include:

- Better adherence to treatment
- Less risk of treatment discontinuation due to adverse effects
- Greater patient satisfaction with treatment
- Reduced anxiety
- Greater receptiveness to treatment adjustment as part of a treat-to-target strategy

What strategies might be used to engage patients with their treatment?

A range of strategies may be used to help patients participate in shared decision making and take responsibility for optimising their chances of treatment success. These include keeping appointments for hospital visits, taking medication regularly, and engaging with lifestyle modifications such as stopping smoking. Telephone contact led by nurses may be helpful for some patients.[18] In a pilot project, three main themes arose from telephone discussions: feelings of being overwhelmed by the rheumatoid arthritis diagnosis; fearing the effects of the disease; and appreciating this personal connection.[18]

Tools designed specifically to enrich shared decision making and empower patients have been described.[19,20] One web-based tool helped patients explore the treatment options clinically appropriate for them after having had an initial conversation with their clinician. The website allowed patients to compare the drugs discussed with their clinicians, and contained exercises to help them understand their own preferences and crystallise their concerns and questions. Other tools may focus on clarifying the patient's attitudes towards different aspects of drug therapy and their risk profile – a so-called value clarification tool.[19]

Using a value clarification tool for patients can help with shared decision making without taking additional consultation time.[19]

In one study, patients were given a simple tool to help them identify what mattered to them most and least about medications for rheumatoid arthritis e.g. aversion to very small risks of a life-threatening adverse effect, avoidance of injections.

- *Using the tool increased the number of visits in which patients expressed their values or preferences when considering different treatment options.*
- *More clinicians were able to base their recommendations on the patient's stated priorities.*

Good practice points

Make the time to discuss the following topics with your patient as part of shared decision making
Fears, beliefs, hopes and expectations • Allay unfounded concerns • Encourage a positive but realistic outlook • Incorporate patient preferences into the treatment plan • Be sympathetic to aspects of treatment that may subjectively affect the quality of life of an individual
Routes of MTX administration • Discuss the pros and cons of tablets and subcutaneous injections
Speed of response to MTX • Let the patient know how long it is likely to be before they can expect to feel the full benefits of MTX
Potential toxicities of MTX • Explain the potential toxicities, the size of the risk and mitigation strategies with regular blood monitoring
Potential tolerability issues • Reassure the patient that although gastrointestinal adverse effects are common, these can be ameliorated with folic acid supplementation or by using subcutaneous MTX
Family planning • If appropriate, explain the need for contraception during MTX treatment • Discuss the approach to MTX interruption if a woman plans to have a child in the future
Vaccinations • Planning for seasonal and non-seasonal vaccinations • Vaccinations for travel destinations
Alcohol consumption
Smoking
Drug interactions • Warn about the risks of over-the-counter NSAIDs

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Optimising MTX treatment for patients with rheumatoid arthritis: summary

What are the key practical steps that can help improve outcomes with MTX treatment?

Proactively optimise every individual's use of MTX with the following management approaches	
Overall treatment strategy	• Treat early and treat-to-target, setting goals and modifying therapy promptly if the targets are not met in a pre-specified time • Share decision making with the patient
Behavioural/lifestyle modifications	• Facilitate smoking cessation • Motivate patients to limit alcohol consumption • Manage anxiety and depression • Educate the patient on how they can give MTX the best chance of success
Optimal dosing	• Start at the right dose – Generally, 10–15 mg/week, depending upon the individual – No need to start with higher doses • Make a choice with the patient between tablets and subcutaneous injections • Escalate the dose as quickly as tolerated – Titrate the dose according to the patient's clinical response – Aim to reach ≥20 mg/week after 6 months – Refer to local guidelines and consider the clinical context • Switch to subcutaneous injections for doses >15 mg/week to enhance MTX bioavailability
Prevention and management of adverse effects	• Prescribe folate supplements – Folic acid at ≥5 mg/week up to 5 mg/day, with the rule that it should never be taken on the same day as MTX – Folinic acid at <7.5 mg/week taken weekly the day after MTX dosing • Advise patients on risk mitigation through blood monitoring according to local protocols • Be aware of potential drug-drug interactions – Explain the need for patients to check with their rheumatologist for compatibility of MTX with over-the-counter drugs, or drugs prescribed by another clinician • In cases of poor gastrointestinal tolerability, switch to the subcutaneous route of administration
Management of inadequate responses	• Allow adequate time for the maximum clinical benefits of MTX to take effect – Use systemic or intra-articular glucocorticoids to bridge the time to maximum effect – Educate the patient as part of shared decision making • Improve MTX bioavailability by dividing oral doses or switching to subcutaneous injections • Consider adding another csDMARD, a bDMARD or a tsDMARD – Do not stop MTX or reduce the dose unless there are toxicity or tolerability issues

Glossary of abbreviations and acronyms

ACR American College of Rheumatology

ACR-N Numeric index of the ACR response

AICAR 5-Aminoimidazle-4-carboxamide ribonucleotide

ALT Alanine aminotransferase

AST Aspartate aminotransferase

bDMARD Biological DMARD

CAMERA Computer Assisted Management in Early RA

CareRA Care in Early Rheumatoid Arthritis

CATCH CAnada-wide early arThritis CoHort

CI Confidence interval

COMET Combination Of Methotrexate and Etanercept in active Early RA Trial

CONCERTO Study to determine the effects of different doses of methotrexate when taken with adalimumab in subjects with early rheumatoid arthritis

csDMARD Conventional synthetic DMARD

CT Computerised tomography

DAS Disease Activity Score

DAS28-ERS Disease Activity Score-28 with erythrocyte sedimentation rate

DHFR Dihydrofolate reductase

DMARD Disease-modifying anti-rheumatic drugs

ERAN Early Rheumatoid Arthritis Network

ERAS Early Rheumatoid Arthritis Study

ESPOIR Etude et Suivi des POlyarthrites Indifférenciées Récentes

EULAR European League Against Rheumatism

FDA Food and Drug Administration

HCQ Hydroxychloroquine

HIV Human immunodeficiency virus

IFN Interferon

IL Interleukin

IM Intramuscular

IR Inadequate response

iRAMT Infliximab Rheumatoid Arthritis Methotrexate Tapering

JESMR Etanercept on Active Rheumatoid Arthritis Despite Methotrexate Therapy in Japan study

MENTOR MEmbranous Nephropathy Trial Of Rituximab

MMP Matrix metalloproteinase

mTSS van der Heijde-modified Total Sharp Scoring system

MTX Methotrexate

MUSICA A study to determine the effect of methotrexate dose on clinical outcome and ultrasonographic signs in subjects with moderately to severely active rheumatoid arthritis treated with adalimumab

NSAID Non-steroidal anti-inflammatory drug

NS Not specified

NWM Network meta-analysis

OD Odds ratio

OPTIMA Study of the optimal protocol for methotrexate and adalimumab combination therapy in early rheumatoid arthritis

ORAL Strategy Oral Rheumatoid Arthritis Trial Strategy

PI Prescribing information

RA Rheumatoid arthritis

RA-Begin A study to evaluate the efficacy and safety of baricitinib in patients with moderately to severely active rheumatoid arthritis who have had limited or no treatment with DMARDs

RCT Randomised controlled trial

REASON RhEumatoid Arthritis SynOvial tissue Network

ROS Reactive oxygen species

SDAI Simplified Disease Activity Index

SmPC Summary of product characteristics

SSZ Sulfasalazine

SURPRISE SUccess of tocilizumab in RA Patients with Remission Induction and Sustained Efficacy after discontinuation

SWEFOT The Swedish pharmacotherapy study

TEAR Treatment of Early Aggressive Rheumatoid arthritis

TEMPO Trial of Etanercept and MTX with radiographic Patient Outcomes

TNF Tumour necrosis factor

TRACTION Treat-to-target in RA: Collaboration To ImprOve adoptioN and adherence

tsDMARD Targeted synthetic DMARD

ULN Upper limit of normal

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