

Recommendations for optimizing methotrexate treatment for patients with rheumatoid arthritis

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Abstract: Methotrexate (MTX) remains the cornerstone therapy for patients with rheumatoid arthritis (RA), with well-established safety and efficacy profiles and support in international guidelines. Clinical and radiologic results indicate benefits of MTX monotherapy and combination with other agents, yet patients may not receive optimal dosing, duration, or route of administration to maximize their response to this drug. This review highlights best practices for MTX use in RA patients. First, to improve the response to oral MTX, a high initial dose should be administered followed by rapid titration. Importantly, this approach does not appear to compromise safety or tolerability for patients. Treatment with oral MTX, with appropriate dose titration, then should be continued for at least 6 months (as long as the patient experiences some response to treatment within 3 months) to achieve an accurate assessment of treatment efficacy. If oral MTX treatment fails due to intolerance or inadequate response, the patient may be “rescued” by switching to subcutaneous delivery of MTX. Consideration should also be given to starting with subcutaneous MTX given its favorable bioavailability and pharmacodynamic profile over oral delivery. Either initiation of subcutaneous MTX therapy or switching from oral to subcutaneous administration improves persistence with treatment. Upon transition from oral to subcutaneous delivery, MTX dosage should be maintained, rather than increased, and titration should be performed as needed. Similarly, if another RA treatment is necessary to control the disease, the MTX dosage and route of administration should be maintained, with titration as needed.

Keywords: bioavailability, dosing, gastrointestinal, polyglutamation, subcutaneous

Plain language summary

Methotrexate is one of the mainstays of treatment for rheumatoid arthritis. It reduces pain and swelling and can slow joint damage and disease progression over time. Most rheumatologists use methotrexate as initial therapy for patients with rheumatoid arthritis, and most patients take it by mouth. Typically, people will start with a weekly dose of 7.5–10 mg and the dose might be raised to 25 mg/wk. There is a relationship between methotrexate dose and its effectiveness for treating the symptoms of rheumatoid arthritis. When methotrexate pills do not control the symptoms of rheumatoid arthritis, it can be administered by an injection beneath the skin. With this approach, more drug reaches the blood without increasing side effects. For some patients, methotrexate alone is not sufficient to control symptoms no matter how it is delivered. In these cases, it can be given with other drugs, including sulfasalazine and/or hydroxychloroquine. Methotrexate might also be combined with biologic medications that include tumor necrosis factor inhibitors and agents that target other inflammatory cells and molecules, such as abatacept and tocilizumab. Regardless of how methotrexate is

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administered or combined with other medications, taking it as prescribed is essential for gaining and maintaining control over rheumatoid arthritis.

Introduction

Methotrexate (MTX) remains the anchor disease-modifying antirheumatic drug (DMARD) for the treatment of rheumatoid arthritis (RA). MTX has multiple mechanisms of action that contribute to improvement in clinical symptoms and disease control in patients with RA, including inhibition of inflammatory cell proliferation, interference with T-cell activity and cytokine secretion, and augmented release of adenosine, which in turn activates receptors on macrophages and neutrophils to decrease the release of proinflammatory cytokines (eg, tumor necrosis factor [TNF]- α and interleukin [IL]-6) and elevate the secretion of anti-inflammatory molecules (eg, IL-10).¹

Current guidelines recommend initially treating early RA (ie, <6 months) and established RA with DMARDs.²⁻⁴ Although MTX is the initial drug of choice for most patients with RA, this medication is contraindicated for some individuals (Table 1).⁵ Moreover, certain patient characteristics may prompt initial use of other DMARDs or biologic agents rather than MTX. These characteristics include prognostic markers for severe disease, extra-articular manifestations of RA, and comorbid conditions. Biomarkers associated with more severe RA include rheumatoid factor and anticitrullinated protein antibodies as well as upregulated acute-phase reactants, particularly C-reactive protein. In addition, functional limitations, extra-articular organ involvement (eg, skin, eye, lung, heart, renal system, nervous system, or gastrointestinal system) and the presence of radiographic joint erosions are indicative of poor

Table 1 Patient characteristics that contraindicate prescription of MTX⁵

Women who are pregnant or breastfeeding
Heavy alcohol users
Patients with
• Alcohol-induced or other chronic liver diseases
• Immunodeficiency
• Renal insufficiency
• Anemia, leukopenia, or thrombocytopenia
• Hypersensitivity to MTX
• Lung disease (eg, pneumonitis or interstitial lung disease of unknown cause)
• Active bacterial or herpes zoster infection, active tuberculosis, or life-threatening fungal infection

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Abbreviation: MTX, methotrexate.

prognosis.^{6,7} Interestingly, several factors predict that MTX monotherapy will manage clinical symptoms and slow radiographic progression, such as male gender, low disease activity, low level of matrix metalloproteinase 3, and lack of prior DMARD use.^{8,9}

Although treatment guidelines clearly support the use of MTX in patients with RA, MTX use has evolved and providers need updated practical information on drug delivery. This review updates practitioners on the evolution of MTX treatment, suggests a paradigm shift in MTX employment, and provides pathways for more effective MTX usage.

Evolution of MTX treatment

Rheumatologists have been using MTX since the 1980s when it began to supplant older treatments, such as penicillamine, sulfasalazine, and gold injections.¹⁰ Interestingly, MTX was used cautiously in patients with RA after it had come off patent for cancer treatment, even before it received US Food and Drug Administration approval for this indication.¹⁰ Notably, MTX was an inexpensive oral tablet and generated little interest for funding of clinical trials. As a result, optimal dosing for MTX in RA was not established and low doses were generally delivered due to concerns about adverse events observed in patients receiving the drug for cancer treatment.¹⁰ Several studies carried out in the mid-1980s demonstrated the efficacy of MTX in RA, but it was larger clinical trials in which MTX was compared with biologics that highlighted the effectiveness of the drug.¹⁰ Results from these studies also suggested that MTX may be underdosed.¹¹ In addition, analysis of treatment patterns carried out since the advent of biologics has shown that patients initially treated with MTX often prematurely switch to a biologic medication or have a biologic added to their treatment regimen.¹² Since the introduction of TNF inhibitors in the late 1990s, there has been a gradual change in how MTX is used in clinical practice, with less aggressive dosing, shorter duration of use, and more rapid escalation to biologics.¹¹⁻¹⁸ For patients starting treatment with a TNF inhibitor, concomitant use of MTX is also declining.^{12,16} The results of surveys and claims analyses have shown that MTX is administered orally in ~95% of patients and that the maximum dosage usually is 15 mg/wk.^{12,14} Switching from oral MTX or addition of a biologic occurs within 6 months of MTX initiation in 51% of patients and within the first month for 25%.¹² Another claims analysis indicated increased administration of biologics as initial treatment for RA (27% of patients in 2009 and 36% in 2012) and reduced use of MTX along with biologic therapy (91% in 2009 vs 79% in 2012).¹⁶ Analysis of RA-related claims from 2008 to 2010 indicated that only 1–15% of patients receiving

nonbiologic monotherapy were switched to a biologic during 1 year of follow-up.^{19,20} This percentage is much smaller than that for patients who initiated treatment with MTX in 2009 or 2012.^{12,16} Results from a recent survey carried out in Italy, which included information from 1,336 RA patients, indicated that <40% had started treatment with MTX within 3–6 months from the diagnosis.²¹ This survey also indicated that only 15.5% of patients being treated with MTX were receiving adequate doses (≥ 15 mg for oral administration and >12 mg for the parenteral delivery).²²

The declining use of MTX may be attributed, in part, to the perception that biologic agents are more precisely targeted to molecules and pathways involved in RA. However, the results of several studies indicate that MTX interferes with multiple inflammatory pathways thought to contribute to RA. MTX undergoes polyglutamation within cells, and MTX and its polyglutamates (MTX-PGs) inhibit purine and pyrimidine synthesis, reduce antigen-dependent T-cell proliferation, and promote release of adenosine, which also has anti-inflammatory activity.²³ The adenosine 2_A receptor is expressed on many immune cells, including neutrophils, monocytes, macrophages, T cells, and natural killer cells. Activation of this receptor increases adenylyl cyclase activity, elevates intracellular levels of cAMP, and inhibits proinflammatory nuclear factor κB and JAK/STAT signaling pathways. These intracellular events serve to decrease proinflammatory cytokines, such as TNF- α and IL-6, and increase the anti-inflammatory cytokine IL-10.^{23,24} Given our increasing understanding of the clinical benefits of MTX and its multiple anti-inflammatory actions, it is surprising that use of this DMARD is declining and that patients are being transitioned from MTX after a shorter period than is recommended.^{25,26}

Shifting the paradigm for MTX treatment

MTX provides long-term clinical benefit for patients with RA

Clinical studies and meta-analyses have demonstrated that patients with RA achieve long-term clinical and structural benefits from MTX. Meta-analysis of results from 7 clinical trials (732 patients, treatment duration 12–52 weeks, and MTX dosage 7.5–25 mg/wk; Table 2) in which MTX was compared with placebo indicated that MTX monotherapy produced clinically important and significant improvements in the American College of Rheumatology (ACR) 50 response rate.²⁷ Radiographic progression, represented by an increase in erosion of >3 units on a scale from 0 to 448, was significantly lower for patients who received MTX versus placebo. In

Table 2 MTX dosing in 7 studies included in a meta-analysis of efficacy

No of patients	MTX dose	Duration
12	20–25 mg/wk	27 weeks
33	10 mg/m ² /wk	18 weeks
132	7.5–15 mg/wk	12 weeks
28	15 mg/wk	12 weeks
482	7.5–15 mg/wk	52 weeks
35	15 mg/wk	12 weeks
189	7.5–15 mg/wk	18 weeks

Note: Data from Lopez-Olivo et al.²⁷

Abbreviation: MTX, methotrexate.

contrast, total Sharp scores were similar for MTX and placebo groups. This meta-analysis also indicated that patients who received MTX monotherapy were twice as likely to discontinue treatment because of adverse events (MTX group, 16%; placebo group, 8%). However, there were no significant differences in the frequency of serious adverse events between the MTX and placebo groups. By 52 weeks, more patients in the MTX group had improved by $>20\%$ on the Medical Outcomes Study Short Form-36 physical component.²⁷

In another meta-analysis, oral MTX monotherapy was compared with MTX in combination with a biologic agent or with additional synthetic DMARDs.²⁸ The analysis included results from 158 clinical trials and more than 37,000 patients. MTX was administered at dosages >15 mg/wk in 35% of trials (18,537 patients). Twenty-nine of these studies included results for a total of 10,697 MTX-naïve patients. Results from this meta-analysis indicated that combinations of MTX with any of several biologic DMARDs (eg, abatacept, adalimumab, etanercept, infliximab, rituximab, or tocilizumab) or tofacitinib were statistically superior to oral MTX alone for achievement of ACR50. The estimated probability of ACR50 with combination therapy ranged from 56% to 67%, compared with 41% for MTX monotherapy. Eighteen trials that together included 7,594 patients addressed radiographic progression with oral MTX monotherapy versus combination treatment. Results indicated that MTX plus adalimumab, certolizumab, etanercept, or infliximab was associated with a significant reduction in radiographic progression relative to oral MTX monotherapy. However, effect sizes for all comparisons were small, and the mean difference between MTX monotherapy and combination treatment (2.34 points over 1 year) was less than the minimal clinically important difference of 5 units on the Sharp-van der Heijde scale.²⁸

Results from several large-scale clinical trials have shown that approximately one-fifth of patients respond to MTX monotherapy in a manner equivalent to that of patients receiving combination treatment.^{29–37} Results from the Trial

of Etanercept and MTX with Radiographic Patient Outcomes (TEMPO) indicated that ~20% of patients on MTX monotherapy achieved and maintained disease remission for at least 2 years^{29,30} and that ~70% of patients who received MTX had no radiographic progression during 3 years of follow-up (Figure 1).³¹ In the Treatment of Early RA (TEAR) trial, 755 participants with early-stage RA associated with poor prognosis were randomized to receive MTX monotherapy or combination treatment (MTX plus etanercept or MTX plus sulfasalazine and hydroxychloroquine). Participants who received MTX monotherapy were transitioned to combination therapy at 24 weeks if the Disease Activity Score for 28 Joints (DAS28) according to erythrocyte sedimentation rate (ESR) was ≥ 3.2 . Of the 370 evaluable participants in the initial MTX monotherapy group, 28% achieved low levels of disease activity and did not require combination treatment. At 102 weeks, the mean DAS28-ESR for these patients was 2.7 versus 2.9 for patients who received combination therapy for the entire treatment period. Patients maintained on MTX monotherapy had less radiographic progression at week 102 than those who received immediate combination therapy (mean Sharp score = 0.2 vs 1.1).^{32,33} Results from the Swedish Pharmacotherapy Trial (SWEFOT) showed that 78% of patients who responded to MTX (DAS28 ≤ 3.2 at 3–4 months) maintained low disease activity or remission for ≥ 2 years.^{34,35} These favorable results with MTX often were obtained in studies in which the oral MTX dosage was not titrated to the level recommended in current guidelines and the patients had not been switched to subcutaneous

MTX from orally administered drug when it did not achieve criterion treatment outcomes.^{36,37}

Rescuing patients for whom oral MTX monotherapy fails

A concern when initiating treatment with MTX monotherapy versus a more intensive combination regimen is whether patients who do not respond to monotherapy will suffer irreversible damage. However, this does not appear to be the case. Results from the TEAR trial indicated that patients initially randomized to receive MTX monotherapy who required transition to combination therapy at 24 weeks (72%) demonstrated DAS28-ESR values (3.5 vs 3.2 at week 48), ACR20/50/70 responses (Figure 2), and radiographic progression (ie, a change in modified Sharp score; 1.2 vs 1.1 at week 102) similar to those for patients who were initially randomized to receive combination therapy or who could be managed with MTX alone.³³ In contrast, results from the HOPEFUL 1 trial (ie, Adalimumab, a Human anti-TNF Monoclonal Antibody, Outcome Study for the Persistent Efficacy Under Allocation to Treatment Strategies in Early RA), in which 333 MTX-naïve patients received adalimumab plus MTX for 52 weeks or MTX monotherapy for 26 weeks followed by 26 weeks of combination treatment, indicated greater radiographic progression among patients whose treatment was escalated to combination therapy (change in total Sharp score over 52 weeks, 3.30 vs 2.56 points).³⁵ This difference may relate to the fact that, in the HOPEFUL 1 study, the maximum permitted MTX dosage was 8 mg/wk.³⁸

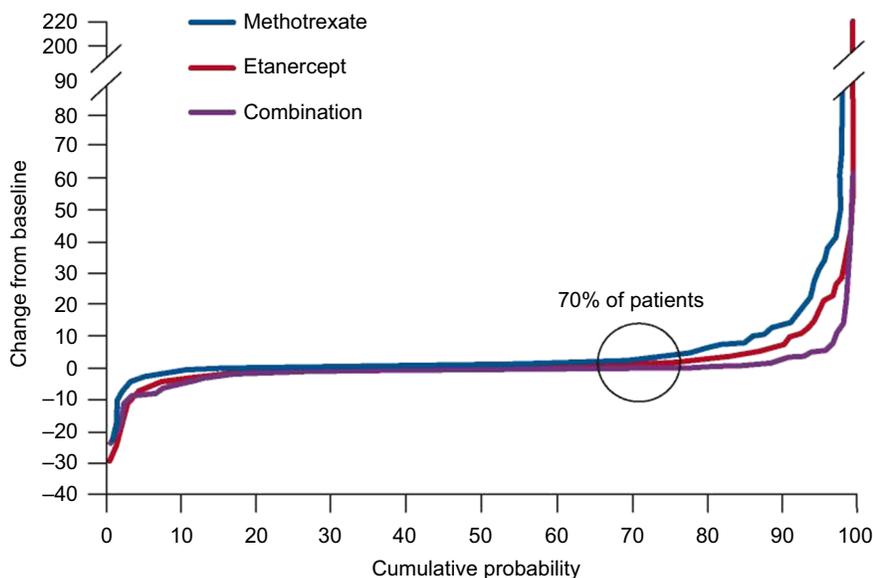


Figure 1 Results from the TEMPO trial at 3 years of follow-up: probability plots of changes in total Sharp scores.

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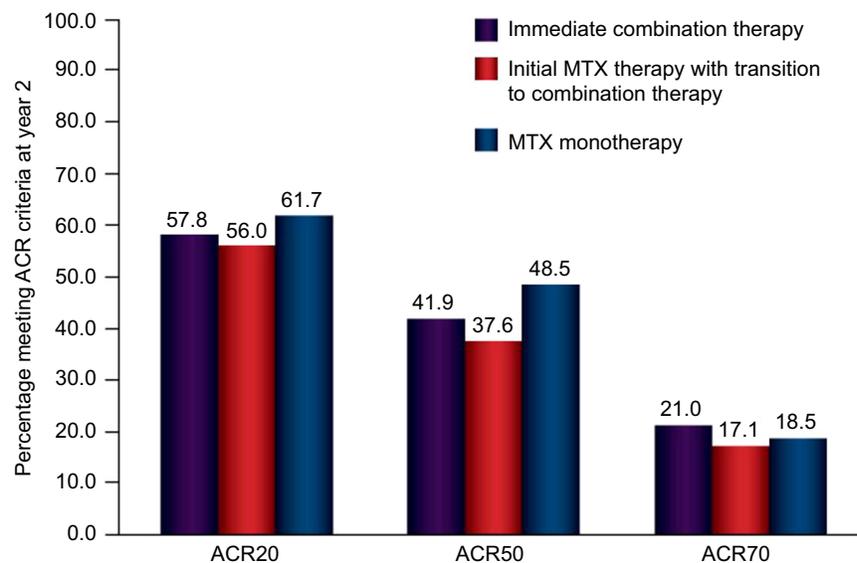


Figure 2 Percentages of patients who achieved a response according to ACR20/50/70 criteria after 2 years of treatment in the TEAR trial.

Notes: Patients received immediate combination therapy, initial MTX therapy with transition to combination therapy, or MTX monotherapy. There were no statistically significant differences among groups. Republished with permission of John Wiley and Sons Inc., from O'Dell JR, Curtis JR, Mikuls TR, et al. Validation of the methotrexate-first strategy in patients with early, poor-prognosis rheumatoid arthritis: results from a two-year randomized, double-blind trial. *Arthritis Rheum.* 2013;65(8):1985–1994. © 2013, American College of Rheumatology, permission conveyed through Copyright Clearance Center, Inc.³³

Abbreviation: ACR, American College of Rheumatology; MTX, methotrexate.

Thus, patients who do not respond to MTX initially and undergo escalation of treatment are able to “catch up” to those who started on a more intensive treatment regimen. It is also worth noting that when used for >1 year, MTX decreases mortality by 70% among patients with RA, even among those who ultimately switch to another therapy.³⁹

Pathways for optimizing MTX treatment

Dosage recommendations for oral MTX

The European League Against Rheumatism (EULAR) recommends a maximum MTX dosage of 20–30 mg/wk but provides no recommendations for titration.³ Spanish guidelines for the treatment of RA recommend an initial dosage of at least 10 mg/wk. For patients with inadequate responses to this regimen, Spanish guidelines specify rapid escalation to 15–20 mg/wk or even 25 mg/wk, over ~8 weeks, with increments of 2.5–5 mg.⁴⁰ ACR guidelines for RA treatment provide no dosage recommendations for MTX.² Results from a systematic review indicated better clinical efficacy when oral MTX was started at 15 mg/wk and escalated at 5 mg/mo to 25–30 mg/wk, which is regarded as the highest tolerable dosage.⁴¹ However, the review showed substantial overlap in results for higher and lower MTX dosages. A more recent study indicated that it may not be possible to define the lowest effective dosage for oral MTX in patients with RA.⁴² This may be attributable to the highly variable absorption of oral MTX. Results from a study in which 41 patients

with RA received the same dosage of MTX intravenously and orally indicated that oral bioavailability ranged from ~20%–>100%.⁴³ This variability can be ascribed, at least in part, to polymorphisms in the gene *SC19A1*, which encodes a reduced folate transporter (RFC) that mediates movement of MTX from the intestine into the bloodstream.^{44,45}

The EULAR guidelines recommend administration of folic or folinic acid for patients who receive MTX.³ Folic or folinic acid can significantly reduce the incidence of gastrointestinal side effects and hepatic dysfunction (determined by measuring serum transaminase levels) and reduces the likelihood that patients will discontinue MTX treatment for any reason.⁴⁶ Whittle and Hughes suggest that folic or folinic acid be administered the day after MTX to avoid competition between folate and MTX for transport from the intestine to the bloodstream.⁴⁷ Simultaneous administration of folic acid and MTX significantly decreases the clinical efficacy of MTX, as reflected by Ritchie Index scores, patients' reports, and physician's global assessments.⁴⁸

Can we be more aggressive with dosing oral MTX?

Some evidence supports a clinical benefit associated with delivery of higher dosages of oral MTX for patients with RA. This potential benefit must be weighed against the possibility of dosage-related adverse events with MTX. Results from several clinical trials have indicated that adverse events with oral MTX are not related to dosage. In a study of 147 patients with RA,

oral MTX was initiated at ≤ 15 or 25 mg/wk, and the higher dosage was not associated with a greater frequency of clinical adverse events or laboratory abnormalities.⁴⁹ Results from a retrospective review of 969 patients with RA who received conventional DMARDs indicated that those who received <10 mg/wk of MTX had a greater frequency of adverse events than those treated with higher dosages.⁵⁰ A randomized, double-blind, parallel, single-site, pilot trial that compared 2 starting dosages of MTX (15 and 25 mg/wk) in MTX-naive adults with RA indicated no difference in tolerability.⁵¹

The recommended minimum duration of MTX monotherapy after which response to treatment can be assessed is 9–12 months for patients with polyarticular juvenile idiopathic arthritis (pJIA).^{52,53} For patients with RA, the minimum recommended duration of MTX treatment for determination of a clinical response is 6 months (or 3 months if no improvement is observed).³ For RA, these minimums are consistent with clinical trial results, indicating continued improvement in symptoms throughout this period.⁵⁴ In practice, $>50\%$ of adults with RA are switched from MTX in <6 months, and 25% are transitioned in the first month.¹² These results suggest that physicians can be more aggressive with the MTX dosage and that initial treatment with MTX should be extended to determine the true response to this therapy.

Options for patients who are not effectively treated with oral MTX

Results from large-scale clinical studies indicate that 70%–80% of patients treated with oral MTX monotherapy do not achieve low disease activity.^{29,32} There are 4 options when oral MTX monotherapy fails to produce desired treatment results: 1) switching from oral to subcutaneous MTX administration,^{40,55} 2) adding other conventional DMARDs (eg, hydroxychloroquine, leflunomide, or sulfasalazine),² 3) adding or switching to a biologic agent,² or 4) adding or switching to tofacitinib.² There is significant clinical support for all 4 treatment-advancing approaches in patients whose response to oral MTX monotherapy is inadequate.

Switching to subcutaneous MTX

Results from multiple studies have indicated that switching to subcutaneous MTX significantly improves efficacy for patients in whom oral MTX was inadequate (Figure 3).^{56–58} This benefit likely relates to the higher blood levels of the parent drug (Figure 4) and of long-chain MTX-PGs produced by subcutaneous administration.^{59,60} Higher blood levels of MTX are achieved from subcutaneous delivery because saturable RFC, expressed by intestinal epithelial cells, is bypassed.²³ Blood levels of MTX and of long-chain MTX-PGs correlate

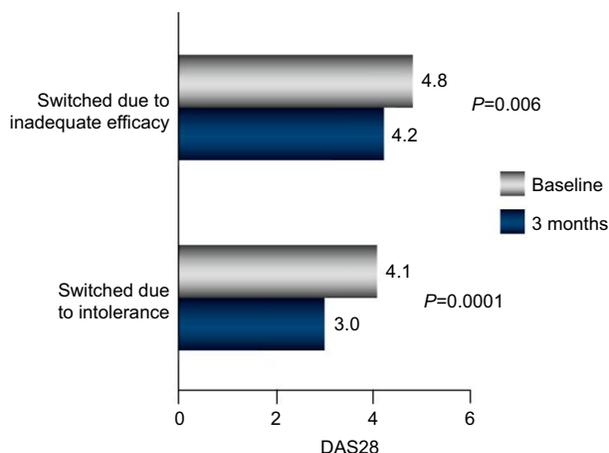


Figure 3 Results of a retrospective analysis of 103 patients with RA.

Notes: Significant improvement in disease control was observed following transition from oral to subcutaneous MTX (40 patients were switched because of inadequate efficacy; 63 were switched because of gastrointestinal side effects). Republished with permission of John Wiley and Sons Inc., from Hameed B, Jones H. Subcutaneous methotrexate is well tolerated and superior to oral methotrexate in the treatment of rheumatoid arthritis. *Int J Rheum Dis.* 2010;13(4):e83–e84. © 2010 Asia Pacific League of Associations for Rheumatology and Blackwell Publishing Asia Pty Ltd, permission conveyed through Copyright Clearance Center, Inc.⁵⁶

Abbreviations: RA, rheumatoid arthritis; MTX, methotrexate; DAS28, Disease Activity Score for 28 Joints.

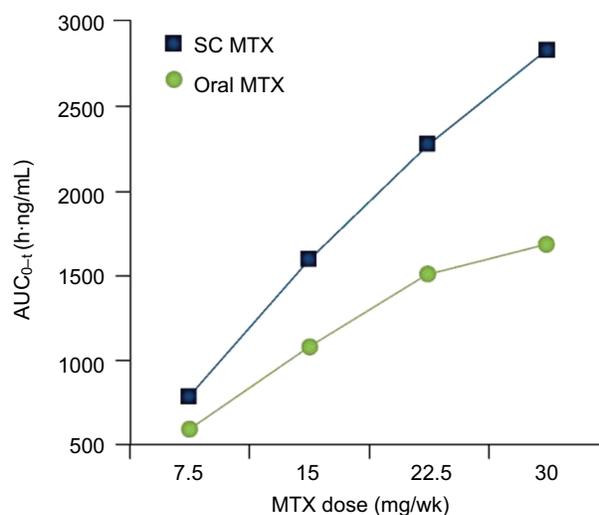


Figure 4 Results from a single-center, open-label, randomized, 2-period, 2-sequence, single-dose, crossover study in 4 dose groups (7.5, 15, 22.5, and 30 mg) with 54 healthy adults treated with oral and subcutaneous MTX.

Note: © 2014 Clinical and Experimental Rheumatology. Reproduced from Pichlmeier U, Heuer KU. Subcutaneous administration of methotrexate with a prefilled autoinjector pen results in a higher relative bioavailability compared with oral administration of methotrexate. *Clin Exp Rheumatol.* 2014;32(4):563–571.⁵⁹

Abbreviations: MTX, methotrexate; SC, subcutaneous; AUC, area under the curve.

significantly with clinical efficacy among patients with RA who receive MTX.^{60–62} When treatment with oral MTX fails, patients are rarely switched to subcutaneous administration. However, O'Dell et al¹² found that 1,808 of 2,511 patients (72%) who were transitioned from oral to subcutaneous MTX were maintained on this treatment for at least 5 years. Results from studies concerned with switching from oral to

subcutaneous MTX have been recently reviewed by Yadlapati and Efthimiou.⁶³

Adding other conventional DMARDs or biologics to MTX

Although supplementation of an oral MTX regimen with 1 or more conventional DMARDs can improve treatment efficacy,^{32,64–66} results from a meta-analysis indicated that such supplementation may not decrease the likelihood of treatment failure resulting from inadequate efficacy.⁶⁵ Many clinical trials have demonstrated that adding or switching to a biologic improves treatment efficacy in patients who have not responded to treatment with oral MTX.^{66–68} Adding a biologic or synthetic DMARD to oral MTX is known to improve outcomes for patients who do not respond adequately to oral MTX alone; however, it is less clear whether either of these treatments is superior to the other. Results from the TEAR trial indicated no significant differences between adding etanercept and adding sulfasalazine plus hydroxychloroquine to an oral MTX regimen among patients for whom oral MTX monotherapy had failed.²⁹ Similar results were reported in the RA: Comparison of Active Therapies in Patients with Active Disease Despite MTX Therapy (RACAT) trial,⁶⁴ and in the SWEFOT, which entailed comparing the addition of infliximab versus the sulfasalazine-hydroxychloroquine combination in patients who did not respond to oral MTX alone.³⁵ In contrast, results from Asia-Pacific Study in Patients to Be Treated with Etanercept or an Alternative Listed DMARD (APPEAL) and Latin RA studies indicated that adding etanercept to oral MTX was significantly superior to adding single-agent hydroxychloroquine, sulfasalazine, or leflunomide for achieving remission or low disease activity according to DAS28-ESR.⁶⁹

Switching to biologic monotherapy in a patient not effectively managed with oral MTX is also a viable treatment alternative. Clinical trial results addressing this approach have recently been summarized in a meta-analysis that included results from 41 randomized clinical trials and 14,049 patients. Results from this analysis indicated that biologic monotherapy significantly improved achievement of ACR50 achievement, function, and remission rates versus placebo or continued treatment or continued MTX/other DMARDs.⁷⁰

Adding or switching to tofacitinib

A meta-analysis of clinical trials indicated that adding tofacitinib significantly improves clinical outcomes for patients with RA whose response to oral MTX monotherapy is inadequate.⁷¹ Tofacitinib monotherapy is also effective for patients with inadequate responses to oral MTX.⁷² Results

from a post hoc analysis of clinical trials indicated that the clinical efficacy of tofacitinib monotherapy is similar to that of combination treatment in patients with inadequate responses to conventional DMARDs, including oral MTX.⁷³

Managing intolerance to oral MTX and improving adherence to therapy

Discontinuation of oral MTX is common. In a retrospective review of 762 patients with RA who were receiving oral MTX, the treatment was discontinued by 260 patients (34%) because of adverse events, including gastrointestinal concerns.⁷⁴ There are several potential approaches to managing adverse events associated with oral MTX: 1) changing the route of MTX administration, 2) reducing the MTX dosage, 3) switching to other conventional DMARDs, and 4) switching to a biologic agent.

Switching to subcutaneous MTX

Switching from oral to subcutaneous administration of MTX has been shown to significantly decrease the frequency of adverse gastrointestinal events in patients with RA.^{75,76} As mentioned previously, switching from oral to subcutaneous MTX is also associated with improved efficacy.^{56–58,75}

Reducing the MTX dosage

Although reducing the dosage has been proposed as a means to mitigate the adverse effects of oral MTX therapy,⁵ this approach has 2 important limitations. First, there is no compelling evidence that the adverse events associated with oral MTX are linked to dosage.^{49,51,77} Second, there is a relationship, albeit weak, between oral MTX dosage and clinical response. Therefore, decreasing the dosage has the potential to negatively impact efficacy.^{41,78}

The risks and benefits of tapering oral MTX treatment for patients with RA have not been well characterized, especially for those who experience adverse events. Three studies that addressed tapering MTX from once weekly to every other week in patients with well-controlled RA indicated that the risk of flares increased following tapering.^{79–81} In 3 other studies, patients for whom MTX provided good control of RA discontinued treatment, which resulted in increased flare rates.^{82–84}

Switching to other conventional DMARDs

Several other conventional DMARDs appear to be less effective than oral MTX, thereby invalidating a switch in treatments.⁵ The long-term radiologic outcomes achieved with oral MTX are superior to those for sulfasalazine,⁸⁵ and the results of a small-scale clinical trial demonstrated significant clinical superiority of MTX over hydroxychloroquine for

patients with RA.⁸⁶ In contrast, leflunomide and MTX had similar efficacy in 2 clinical studies.^{87,88}

Switching to a biologic agent

The efficacy of most biologic agents is enhanced when the agent is administered in combination with MTX, and this benefit, at least for some agents, is dosage related.^{67,89} Therefore, switching from oral MTX to a biologic may be impractical. Moreover, there appears to be no correlation between MTX dosage and toxicity when MTX is combined with a biologic agent.⁹⁰ The IL-6 inhibitor tocilizumab is equally effective when delivered as monotherapy or with MTX in patients whose response to MTX alone was inadequate.⁹¹ This may also be true for tofacitinib.⁷³

Improving patient adherence to MTX treatment

Patients with RA are poorly adherent to MTX treatment

Adherence to oral MTX treatment is often poor. In a study of 251 patients, 105 patients (42%) reported not taking MTX as prescribed.⁹² Reasons for nonadherence in that study included forgetting to take the drug (33%), not needing it when feeling well (24%), and concern about long-term safety (24%). Among the nonadherent patients, 53% took lower doses, 52% skipped doses, and 6% reported other nonprescribed ways of taking MTX.⁹² A study of 6,018 patients for whom DMARDs had been recently prescribed indicated that ~50% of the patients prescribed MTX had stopped this treatment within 1 year; the median time before stopping DMARD therapy was 150 days.⁹³ Similarly, results from a claims analysis of 24,479 patients who underwent MTX treatment indicated that ~50% discontinued it within 1 year.¹⁴

Poor adherence to treatment among patients with RA is not unique to MTX. Results from an analysis of the Tennessee Medicaid databases (1995–2004) that included information for 14,932 patients with RA indicated that persistence with therapy was similar with all nonbiologic DMARDs except sulfasalazine, which had lower persistence.⁹³ In addition, persistence with MTX was similar to that recorded for etanercept and adalimumab and was better than that for infliximab.⁹³

How can we improve patient adherence to MTX?

Results from several studies have indicated that education and counseling significantly improve adherence to therapy for patients with RA who receive conventional DMARDs, including MTX.^{94–96} Furthermore, subcutaneous MTX is

associated with better treatment persistence than oral MTX. Results from the Canadian Early Arthritis Cohort (CATCH) study, which included 666 patients on MTX treatment (417 oral and 249 subcutaneous) indicated that at 1 year, 49% of the patients initially treated with subcutaneous MTX had changed treatment versus 77% of those initially treated with oral MTX.⁹⁷ A retrospective review of the patients who were switched from oral to subcutaneous MTX and had follow-up for 5 years indicated that 50% persisted with subcutaneous treatment for at least 51 months.⁹⁸

Dosing MTX

Oral administration

It has been suggested that oral MTX should be started at 10–15 mg/wk, with gradual escalation by 5 mg every 2–4 weeks to a dosage of 20–30 mg/wk.⁴¹ However, Medley et al⁴⁹ suggest that initiation of oral MTX at 25 mg/wk does not pose greater risk of liver toxicity or other adverse effects versus gradual titration from a low dosage.

Treatment of patients with pJIA may provide important information about MTX dose setting for adults with RA. The recommended starting MTX dosage for children with pJIA is 10–15 mg/m²/wk, which converts to ~0.3–0.6 mg/kg/wk.^{99,100} The corresponding weight-based dose for a 70 kg adult with RA is 0.2 mg/kg (15 mg/wk). This is about one-half the dose administered to patients with pJIA. The recommended duration for MTX monotherapy in patients with pJIA is also longer than that typically used for adults with RA.

Dosing recommendations for switching from oral to subcutaneous MTX

Studies have demonstrated that the bioavailability of a dose of MTX delivered subcutaneously is significantly higher than the bioavailability of an equivalent dose administered orally.^{59,101,102} Therefore, when switching to subcutaneous MTX, the patient should receive the same dose that had been prescribed for oral administration. This will significantly increase MTX exposure.¹⁰³

Initiating treatment with subcutaneous MTX

While patients typically prefer oral versus injected treatment,¹⁰⁴ initiating treatment with subcutaneous MTX versus oral drug is a potentially better option for patients willing to undertake injections. A head-to-head comparison of oral versus subcutaneous MTX in patients with RA indicated significant superiority of subcutaneously administered drug for achievement of ACR20 and ACR70 improvements.¹⁰⁵

Results from the CATCH study also demonstrated better clinical efficacy and better persistence with subcutaneous MTX versus oral drug,⁹⁷ and that treatment with subcutaneous MTX delays progression to a biologic agent versus oral drug.¹⁰⁶ All of these results support the view that initiating treatment with subcutaneous MTX has the potential to provide superior clinical outcomes versus oral drug and delay progression to more expensive biologic therapies.

Dosing MTX when combined with a TNF inhibitor

Supplementing MTX treatment with a TNF inhibitor is more effective than switching to TNF inhibitor monotherapy; however, guidance is lacking for MTX dosing in this setting. A post hoc analysis of results from the TEMPO and Combination of MTX and Etanercept in Active Early RA (COMET) trials, in which patients were grouped according to the MTX dosage administered in combination with etanercept (<10.0, 10.0–17.5, or >17.5 mg/wk), indicated no differences among the study groups for numerous metrics: achievement of DAS28 remission or low disease activity (Figure 5), ACR20/50/70 responses, Health Assessment Questionnaire-Disability Index scores, or quality of life.¹⁰⁷ In contrast, patients with early-stage RA who were treated with combination therapy in the CONCERTO trial (ie, Study to Determine the Effects of Different Doses of MTX When Taken with Adalimumab in Subjects with Early RA) had better clinical outcomes with a high MTX dosage plus adalimumab if they had not received MTX previously.⁸⁹ Neither of these studies directly addressed whether the MTX dose could be reduced upon adding a TNF inhibitor, without compromising treatment efficacy. The Dutch RA Monitoring (DREAM) registry included information of 458 patients (34%) who underwent tapering of MTX, 126 patients (10%) who discontinued MTX, and 747 patients (56%) who maintained their MTX dosage after adding a TNF inhibitor for the first time. This registry showed no differences in DAS28 results for the 3 groups during 24 months of follow-up.¹⁰⁸ Similarly, results from the Infliximab RA MTX Tapering (iRAMT) trial indicated that reducing the MTX dosage after adding infliximab did not adversely affect the outcomes for ~75% of patients.¹⁰⁹

Summary recommendations for MTX optimization

This review supports several recommendations for optimizing MTX therapy for patients with RA:

- Administration of a high initial dose of MTX followed by rapid titration can improve the response to oral MTX and does not appear to compromise safety or tolerability.

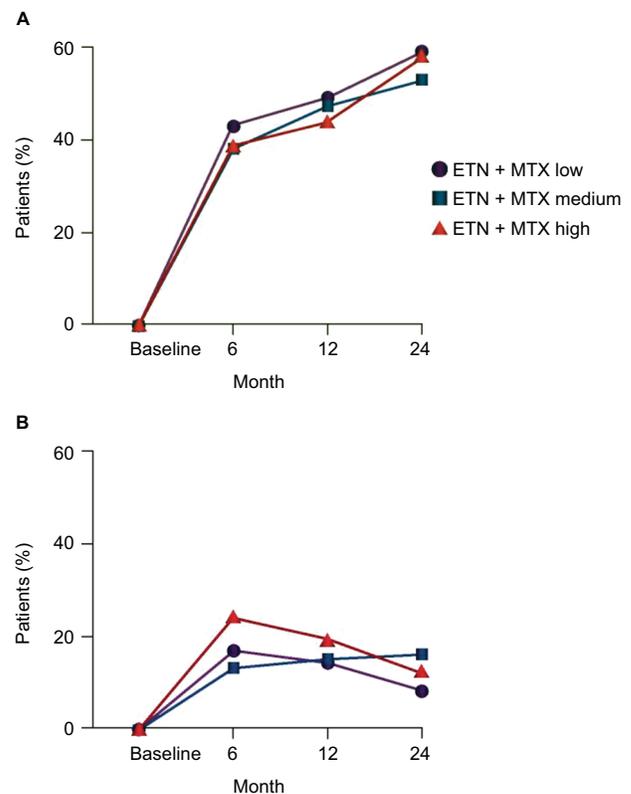


Figure 5 Percentage of patients achieving (A) DAS28 remission and (B) DAS28 low disease activity at baseline and at 6, 12, and 24 months.

Note: DAS28 remission was defined as DAS28 <2.6; low disease activity was defined as DAS28 >2.6 and <3.2. Reproduced from Gallo G, Brock F, Kerkmann U, Kola B, Huizinga TW. Efficacy of etanercept in combination with methotrexate in moderate-to-severe rheumatoid arthritis is not dependent on methotrexate dosage. *RMD Open*. 2016;2(1):e000186. Copyright © 2016 with permission from BMJ Publishing Group Ltd.¹⁰⁷

Abbreviations: DAS28, Disease Activity Score for 28 Joints; ETN, etanercept; MTX, methotrexate.

- Treatment with oral MTX, with appropriate dose titration, should be continued for at least 6 months to accurately assess clinical response (if the patient has experienced any response to treatment by 3 months).
- Patients for whom MTX treatment fails because of intolerability or inadequate efficacy may be “rescued” by switching to subcutaneous MTX.
- Consideration should also be given to starting with subcutaneous MTX given its favorable bioavailability and pharmacodynamic profile.
- Starting patients on subcutaneous MTX or switching from oral to subcutaneous delivery is likely to improve treatment persistence.
- If a patient is switched from oral to subcutaneous MTX, a concomitant dosage increase should be avoided. After the change in delivery route, the dose may be titrated as needed.
- If a patient has tolerated MTX monotherapy but has not responded adequately, the patient may also be prescribed another agent. In such cases, the MTX dosage and route

of administration used before treatment augmentation should be maintained, with titration as needed.

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Disclosure

Alfonso Bello served as a speaker for Abbvie, speaker and advisory board for Pfizer and Medac Pharma, and consultant and speaker for Horizon Pharma and Mallinckrodt. Elizabeth Perkins served as a consultant for Medac Pharma, Pfizer Inc, Lilly, USA, LLC, Amgen Inc, and Antares Pharma Inc. Randy Jay served as a consultant for Medac Pharma. Petros Efthimiou served as a speaker and consultant for Medac Pharma. The authors report no other conflicts of interest in this work.

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