Because of its efficacy and safety, methotrexate (MTX) is well established as the anchor drug for treatment of rheumatoid arthritis. Although MTX is typically administered orally, parenteral MTX offers greater bioavailability and may cause less gastrointestinal intolerability. Parenteral MTX may be considered for patients with rheumatoid arthritis who experience an inadequate response to oral MTX at the highest tolerated dose; however, its use remains low in the USA. To facilitate the administration of subcutaneous MTX, a state of the art MTX auto-injector that enables patients to self-administer prespecified doses of MTX subcutaneously was recently developed. This auto-injector may improve patient adherence and the ability to reach an optimally effective MTX dose, thereby allowing more patients with rheumatoid arthritis to obtain the maximum benefit from MTX.

**Keywords:** auto-injector • bioavailability • disease-modifying antirheumatic drug • dose optimization • rheumatoid arthritis • self-administration • subcutaneous methotrexate

Methotrexate (MTX) has been recognized as a valuable treatment for rheumatoid arthritis (RA) for more than 30 years and, despite the emergence of many newer therapies, remains the cornerstone of RA treatment [1]. Current guidelines from both the ACR [2] and the European League Against Rheumatism (EULAR) [3] recommend MTX as first-line therapy for RA, either alone or in combination with other disease-modifying antirheumatic drugs (DMARDs). MTX is also an important component of long-term therapy, and its use has been shown to be sustained for 5 years or more by greater than 70% of patients with RA [4,5]. The US FDA recently approved a MTX auto-injector (MTXAI; Otrexup™, Antares Pharma, NJ, USA) [6]. This MTXAI provides a mechanism for easy self-administration of subcutaneous (sc.) MTX, and serves as an alternative to standard oral and injectable (via vial, needle, and syringe) MTX formulations. This review focuses on the clinical importance of MTX for the treatment of RA, highlighting the value of sc. MTX in particular, in the context of the new MTXAI.

**Clinical importance of MTX in the treatment of RA**
Owing to its efficacy and safety, MTX has gained wide acceptance as a key treatment option for patients with RA. The emergence of biologic DMARDs has offered additional effective treatment options, delivered either alone or concomitantly with conventional DMARDs; however, the clinical data regarding the relative efficacies of MTX and biologics may have contributed to an underestimation of the efficacy of MTX [7]. Many of the key studies that identified a greater clinical benefit of biologics compared with MTX relied on low (≤20 mg) and rigidly standardized MTX doses [8–11]. Treat to target protocols that allow dose escalation may, however, be critical in maximizing the benefit from MTX [12,13]. Importantly, almost all Phase III trials of biologic agents have used baseline MTX inadequate responders as comparators [14–21]; by selecting for MTX inadequate responders these studies bias patient populations against continued MTX use and are likely to underestimate the effect of MTX.
Despite these common clinical trial limitations, multiple parallel-design studies have been conducted in patients who were naive to MTX and biologics, thereby offering a more accurate comparison of the efficacy of biologics with that of MTX. TEMPO was a randomized double-blind study comparing clinical and radiographic outcomes of MTX, etanercept, and the combination of MTX and etanercept among patients not currently receiving either drug [9]. Previous MTX use was permitted, provided it was not received within 6 months of study enrollment and patients had not experienced toxic effects or a lack of efficacy. Although the combination of MTX with etanercept was found to be the most effective treatment option, the clinical efficacies of MTX and etanercept alone were comparable over the 3-year duration of the study, with no significant differences in mean Disease Activity Score found between MTX and etanercept patients at any time point measured [22]. Additionally, although MTX was associated with greater mean radiographic progression (measured by modified total Sharp score and erosion scores) than etanercept, this difference was driven by a minority of patients. In fact, the majority of patients in both treatment groups (57% for MTX and 68% for etanercept) experienced no radiographic progression (total Sharp score ≤0.5) throughout the study [9].

Similar findings regarding the efficacy of MTX relative to a biologic therapy were observed in the PREMIER trial, a randomized double-blind study comparing the efficacy and safety of MTX, adalimumab, and the combination of MTX and adalimumab among MTX-naive patients [8]. Although the combination of MTX and adalimumab produced the greatest response rates, no significant differences in ACR20, ACR50, ACR70 or ACR90 responses were found between patients treated with adalimumab or MTX alone, measured after either 1 or 2 years of treatment, suggesting a similar degree of clinical efficacy between the two therapies [8]. As was observed with etanercept, MTX monotherapy was associated with greater mean radiographic progression than biologic monotherapy; however, probability plots revealed a similar proportion of patients in the MTX and adalimumab monotherapy groups with significant radiographic progression [23].

Together with other studies [1,12,13–25], TEMPO and PREMIER highlight a high degree of clinical efficacy for MTX in the treatment of RA, which is compatible with the important role that MTX has played within the therapeutic landscape [7,26].

Advantages of subcutaneous MTX for the treatment of rheumatoid arthritis
MTX can be delivered either orally or parenterally, although the vast majority of patients with RA in the USA receive oral treatment [27]. The most common limitations of oral MTX leading to its discontinuation are poor tolerability and inadequate efficacy [5]. Parenteral MTX appears to enable patients to achieve higher concentrations of MTX because of increased bioavailability and tolerability, and may be an underutilized treatment option.

Although generally well tolerated, oral MTX is associated with certain limitations including gastrointestinal (GI) symptoms such as nausea and diarrhea. Although physicians may regard these as ‘nuisance symptoms’, they not infrequently lead to treatment discontinuation. GI symptoms have been reported to cause approximately 13% of MTX treatment discontinuations [5]; however, we estimate an even greater frequency based on our personal clinical experience. GI symptoms may become more apparent over the course of treatment, as MTX doses typically increase [28], and may limit patients’ ability to maintain an optimally effective MTX dose. Switching to parenteral administration has been shown in multiple studies to improve the GI tolerability of MTX and therefore allow higher effective doses to be administered [29–31]. In addition to the GI symptoms of oral MTX, additional safety concerns less frequently leading to treatment discontinuation are common to both oral and parenteral MTX, and include oral ulcers, skin rash and hepatic and hematologic laboratory abnormalities [5].

The ability to achieve higher doses and greater efficacy with parenteral MTX is supported by a large retrospective analysis of patients with RA within the US Veterans Administration database, which analyzed factors associated with MTX dosing patterns and therapeutic decisions [32]. Compared to patients who received oral MTX, patients in this study who were treated with parenteral MTX were found to have achieved higher MTX doses, consistent with greater tolerability. Furthermore, higher maximum MTX doses were associated with a reduced need for additional concomitant therapies [32], suggesting that higher drug exposure achievable with parenteral MTX may have offered enhanced disease control for patients who were unable to increase their oral MTX dose.

Dose optimization of oral MTX is also limited by absorption saturability factors, as the uptake of MTX by the GI tract relies on a saturable transporter, RFC1 [33]. Pharmacokinetic studies have demonstrated that the absorption of MTX decreases by as much as 30% at an oral dose of 15 mg or more compared with parenteral administration [33,34]. Therefore, parenteral administration may provide an opportunity for patients with an inadequate response to high doses of oral MTX to achieve an optimally effective dose.
A randomized double-blind trial conducted across eight sites provided a direct head-to-head comparison of the efficacy and safety of oral versus sc. MTX among 384 MTX-naive patients with active RA [35]. This study randomized patients to receive 15 mg/week oral MTX or 15 mg/week sc. MTX and required patients to switch to 15 mg/week sc. or 20 mg/week sc., respectively, if ACR20 was not achieved after 16 weeks of treatment. A significant benefit of sc. MTX was apparent after 24 weeks of treatment; rates of both ACR20 and ACR70 responses were significantly greater among patients receiving sc. MTX than among those receiving oral MTX (p < 0.05). Furthermore, among the oral MTX ACR20 nonresponders at week 16, switching to an equivalent dose of sc. MTX was associated with a 30% ACR20 response rate at week 24 [35]. The incidence of adverse events was similar between the two groups, although the intensity of adverse event was not evaluated; a previous study, however, had observed a marked decrease in the severity of most GI symptoms after switching to sc. MTX [31].

Multiple studies have concluded that switching to sc. MTX among patients who were intolerant of or inadequately responsive to oral MTX is an effective treatment option. CAMERA was a randomized, 2-year, multicenter strategy trial that compared a conventional MTX treatment strategy, in which dose adjustments were made at the discretion of each rheumatologist, to an intensive MTX treatment strategy, in which dose adjustments were calculated by a computerized decision protocol based on various patient parameters [13]. Among the specifications of the intensive treatment protocol was a requirement that patients switch to sc. MTX when the highest tolerated dose of oral MTX proved inadequate. Among patients who switched from oral to sc. MTX, a significant improvement in Disease Activity Score including 28 joints (DAS28) was observed 1 month after the switch [29]. Furthermore, among these patients, those who switched due to intolerance and those who switched due to inefficacy had comparable improvement [29], suggesting that sc. MTX may be a valuable treatment option for patients regardless of whether they switched from oral MTX because of intolerance or inadequate efficacy.

A retrospective analysis of patients with RA further assessed the clinical benefits of sc. MTX compared with oral MTX, based on treatment protocols established at each treatment center [30]. This study examined 78 patients with RA who received sc. MTX monotherapy after discontinuing oral MTX due to intolerance or inefficacy, matched by disease duration and baseline Disease Activity Score to a control population of 78 patients with RA who received continuous oral MTX monotherapy. Patients receiving sc. MTX experienced significant improvement 6 months after switching from oral MTX: DAS28 improved by 1.2 points or more (a clinically relevant change) in 74% of patients treated with sc. MTX compared with 48% of patients treated with oral MTX (p = 0.035), and low disease activity (DAS28 <3.2) was achieved by 29% of patients treated with sc. MTX compared with 16% of patients treated with oral MTX (p = 0.02) [30]. Taken together, this body of data suggests that sc. MTX may be a valuable and underutilized treatment option for patients with RA, particularly among patients who are intolerant of or inadequately responsive to oral MTX.

**Use of a MTXAI to deliver subcutaneous MTX: bioavailability & safety**

Despite the advantages of sc. MTX, safe and accurate sc. delivery with a standard vial, needle, and syringe may be difficult for many patients with RA, and these difficulties may contribute to the low rate of sc. MTX use, particularly in the USA. Manual dexterity, which may be limited among patients with RA, is required to consistently measure an accurate dose for injection and to prevent accidental needle injury. Additionally, a fear of needles may cause an aversion to injections for some patients. Until recently sc. administration of MTX was not approved for RA in the US, and this delivery option has mainly been reserved for patients who are intolerant of or inadequately responsive to oral MTX. The MTXAI Otrexup allows patients to self-administer prespecified doses of sc. MTX, and was recently developed to accommodate the specific needs of the RA patient population [27,36]. This MTXAI is approved by the FDA [6], and may overcome many of the limitations of standard sc. MTX delivery via vial, needle, and syringe. Unlike standard syringes, the MTXAI is prefilled, requires no movement of the thumb to initiate the injection, and keeps the needle hidden from view throughout the injection process. Similar autoinjectors have been shown to cause less pain than syringes, to be preferred by patients and healthy volunteers [37,38], and to increase long-term treatment adherence [39]. The MTXAI is currently approved for the management of patients with severe, active RA who are intolerant of or had an inadequate response to first-line therapy [6], and may be an important treatment option for patients.

A critical advantage of sc. over oral administration of MTX is its improved systemic exposure. The pharmacokinetics of low-dose MTX has been known for over two decades now [40,41]; however, a head-to-head (oral vs sc. MTX) pharmacokinetic study with commonly used doses to treat RA had until recently not been performed. To delineate the pharmacokinetic
dose exposure with respect to the MTXAI, a randomized, open-label, three-way crossover, Phase II study was conducted that assessed the bioavailability of MTX delivered by the MTXAI, administered either in the abdomen or thigh, to that of oral MTX [27]. The study enrolled 49 adult patients with RA in the USA who had been receiving MTX for at least 3 months; approximately 78% of these patients were receiving oral MTX. Patients were assigned to a MTX dose most consistent with their prior MTX dose and disease status (10, 15, 20 or 25 mg) and received a random sequence of three MTX treatments: oral MTX, MTXAI delivered to the abdomen, and MTXAI delivered to the thigh. Pharmacokinetic analysis demonstrated a bio-equivalence between MTXAI delivered to the abdomen and thigh; however, the bioavailability of oral MTX was consistently lower than that of the MTXAI at each of the four dose levels (Figure 1). Furthermore, whereas systemic exposure increased in proportion to the dose when MTX was delivered by the MTXAI, systemic exposure of orally administered MTX plateaued at ≥15 mg, indicating a significant saturability limitation [27]. These findings suggest that the MTXAI may overcome the dose limitations of oral MTX and may help patients achieve an optimally effective MTX dose.

The pain and the ease of use of the MTXAI were assessed in an open-label Phase II study of 101 patients with RA, each of whom was trained to use the device and successfully completed a single self-injection under the observation of site healthcare personnel [36]. Patients in this study reported minimal pain; mean and median pain scores immediately following self-administration were 3.6 and 1.0, respectively, on a 100-point visual analog scale, in which 0 indicated no pain and 100 indicated the worst pain imaginable. Injection-site erythema was infrequent, with 4–11.7% of patients experiencing very slight or barely perceptible erythema. Patients also reported minimal difficulties with self-administration; 98% of patients agreed or strongly agreed that the ‘device was easy to use’, and 100% of patients indicated that ‘written instructions were clear and easy to follow’. Safety of the MTXAI was also assessed in both Phase II studies, and no unexpected adverse events were identified based on the known safety profile of MTX [27,34]. Together, these Phase II studies support the MTXAI as a safe and easy-to-use option for the sc. administration of MTX to patients with RA, and suggest that this device may provide greater opportunities for dose optimization than oral MTX.

Conclusion
MTX is an integral component of RA treatment and is valuable as both a first-line DMARD and a long-term RA treatment. The value of sc. compared with oral administration of MTX has been highlighted by multiple clinical studies that demonstrate significant advantages in MTX bioavailability and significant clinical benefits to switching from oral to sc. administration in situations of intolerability or inefficacy. A switch to sc. MTX in these circumstances has been recommended as a therapeutic option by both Canadian guidelines [42] and European experts as the result of a systematic literature search into optimal MTX dosing and administration [43]. The use of sc. MTX to optimize dosing may allow more patients to achieve an adequate response to MTX and thereby delay the progression to biologic therapies, which may be important because of cost and safety concerns associated with the use of biologics.

Although sc. administration of MTX is infrequent within clinical practice in the USA, the ease of use and minimal pain associated with the MTXAI may make it a more attractive treatment option for patients with RA. MTX auto-injection may be a valuable treatment option for clinicians to consider and can be viewed as an important tool to facilitate safe and consistent sc. administration.

Financial & competing interests disclosure
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Executive summary

Clinical importance of methotrexate in the treatment of rheumatoid arthritis

• Methotrexate (MTX) is the cornerstone of treatment for rheumatoid arthritis and is used by most rheumatoid arthritis patients, either alone or in combination with additional disease-modifying antirheumatic drugs.
• Although available in both oral and parenteral formulations, MTX is typically delivered orally in the USA.
• The major limitations of oral MTX are gastrointestinal tolerability and absorption saturatability at high doses.

Advantages of subcutaneous MTX for the treatment of rheumatoid arthritis

• Compared to oral administration, subcutaneous administration of MTX provides greater bioavailability, and it may mitigate gastrointestinal distress.
• Switching from oral to subcutaneous administration of MTX when the greatest tolerated oral dose yields an inadequate response may be an effective treatment strategy for patients with rheumatoid arthritis.
• The use of subcutaneous MTX may be limited by patients’ fear of needles, difficulties administering an accurate dose, and manual dexterity limitations.

Use of a MTX auto-injector to deliver subcutaneous MTX: bioavailability & safety

• A MTX auto-injector was recently developed that allows patients to self-administer prespecified doses of MTX subcutaneously.
• The MTX auto-injector was found to provide greater systemic exposure than oral MTX at all doses tested, and was reported by patients to be easy to use and nearly pain-free.
• Self-administration of MTX using the auto-injector may increase treatment adherence among patients with rheumatoid arthritis and may delay the need to progress to biologic drugs.

References
Papers of special note have been highlighted as: • of interest; • of considerable interest

• Current ACR recommendations for the treatment of rheumatoid arthritis.


• Current European League Against Rheumatism recommendations for the treatment of rheumatoid arthritis.


13 Verstappen SM, Jacobs JW, Van Der Veen MJ et al. Intensive treatment with methotrexate in early rheumatoid arthritis:


• Bioavailability study comparing oral methotrexate (MTX) with the MTX auto-injector delivered to the abdomen and thigh.


• Post hoc analysis of the effectiveness of switching from oral to subcutaneous (sc.) MTX owing to inefficacy.


• Retrospective analysis of the effectiveness of switching from oral to sc. MTX owing to intolerance or inefficacy.


- **Head-to-head comparison of the efficacy and safety of oral and sc. MTX.**


- **Actual human use study assessing the pain and ease of use of the MTX auto-injector.**


