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EXPERT REVIEWS

New autoinjector technology for the delivery of subcutaneous methotrexate in the treatment of rheumatoid arthritis

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Michael Schiff*[1], Jonathan Jaffe[2], Bruce Freundlich[3,4] and Patrick Madsen[5]

[1]*Department of Rheumatology, University of Colorado, Denver, CO, USA*
[2]*Clinical Development, Antares Pharma, Inc., Ewing, NJ, USA*
[3]*University of Pennsylvania School of Medicine, Philadelphia, PA, USA*
[4]*Medical Affairs, Antares Pharma, Inc., Ewing, NJ, USA*
[5]*Parenteral Products Division, Antares Pharma, Inc., Minneapolis, MN, USA*
**Author for correspondence:*
Tel.: +1 303 773 8429
michael.schiff@me.com

Methotrexate (MTX) is the cornerstone of treatment for rheumatoid arthritis (RA), and is widely used both as first-line therapy and as an important component of long-term therapy. Although subcutaneous MTX is typically delivered orally, parenteral administration offers benefits with respect to tolerability and systemic exposure, and may be an underutilized treatment option. The RA patient population presents specific challenges for safe and accurate administration of parenteral therapies, because of common symptoms of joint pain and limited manual dexterity. These challenges may contribute to the low incidence of parenteral MTX administration. A novel MTX autoinjector (MTXAI) was recently introduced, which is designed to facilitate subcutaneous MTX self-administration among patients with RA. Here we review the development and utility of the MTXAI in the treatment of RA, and discuss how this technology may facilitate the use of subcutaneous MTX.

Keywords: auto-injector • disease-modifying antirheumatic drug • Otrexup • pre-filled syringe • rheumatoid arthritis • self-administration • subcutaneous methotrexate

Rheumatoid arthritis (RA) is a chronic inflammatory joint disease that affects approximately 1.5 million people in the USA, equivalent to almost 1% of the adult population [1,2]. The inflammatory effects of RA typically manifest as pain, swelling, stiffness and limitations of motion, and are often observed in joints of the fingers, wrists and knees [2]. Although RA cannot be cured by therapeutic intervention, effective treatment options have enabled many patients to achieve low-disease activity or remission, which have become important treatment goals [2–4].

Although major advances in disease outcomes were made possible by the advent of biological agents more than a decade ago, successes in the treatment of RA may also be attributed in large part to the efficacy of conventional disease-modifying antirheumatic drugs (DMARDs). Conventional DMARDs include methotrexate (MTX), hydroxychloroquine, sulfasalazine and leflunomide, and have been shown to be effective in controlling symptoms, improving physical function and slowing the progressive joint damage associated with RA [5]. Conventional DMARDs are recommended by both American and European guidelines as first-line treatment for RA; additional conventional or biological DMARDs may be added for patients with a poor prognosis or an inadequate response to first-line therapy [3,4]. Among the conventional DMARDs, MTX has largely emerged as the drug of choice because of its sustained efficacy as a long-term treatment, high levels of patient retention and manageable safety profile [2]. Worldwide, a majority of patients with RA receive MTX during the course of their treatment [6,7], and MTX is considered by many rheumatologists to be the cornerstone of RA treatment.

MTX can be delivered either orally or parenterally; however, in the USA, MTX is most often administered orally [8]. Oral MTX is generally effective and well tolerated, although the most common limitations are gastrointestinal (GI)

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intolerability and absorption at higher doses [7,9,10]. GI symptoms often include nausea, abdominal pain and diarrhea [11], and are a frequent cause of treatment discontinuation [7]. As an alternative to oral MTX, parenteral MTX offers improved GI tolerability and improved systemic exposure [9–12]. Parenteral therapy appears to be an underutilized treatment option for patients with RA who are intolerant of or have an inadequate response to high doses of oral MTX, particularly in the USA.

The clinical benefit of a switch from oral to parenteral MTX was demonstrated in a randomized trial of MTX-naive patients with RA, in which patients experiencing an inadequate response to oral MTX were required to switch to an equivalent dose of subcutaneous MTX [13]. Following the switch to subcutaneous MTX, many patients who were inadequately responsive to oral MTX were able to achieve significant clinical responses, suggesting that parenteral MTX may benefit many patients who respond inadequately to oral MTX. The clinical utility of this therapeutic switch is further supported by additional studies involving patients with RA who changed their method of MTX administration, in which parenteral MTX was associated with significant clinical benefits over oral MTX [14–16].

Overview of the market

Current use of parenteral MTX

Despite the advantages of parenteral MTX over oral MTX regarding systemic exposure and GI tolerability, an estimated 5% or fewer patients with RA in the USA receive parenteral MTX [8]. Many of the difficulties associated with manual injections involving a standard vial, needle and syringe may be exacerbated by the functional limitations that are common in patients with RA; joint pain and impaired mobility frequently limit patients' ability to complete activities requiring manual dexterity or grip strength, such as typing, writing or holding a book to read [17,18]. Patients with RA may therefore struggle with manually measuring and injecting a complete MTX dose. Oftentimes these limitations may be overcome with the aid of a spouse or caregiver who can handle the patient's injections; however, risks associated with accidental needle-stick injury, anxiety concerning the use of needles and potential dose inaccuracies may cause patients and physicians to avoid manual MTX injections. Historical shortages in the availability of MTX vials [19,20] may have also contributed to a reluctance among physicians to prescribe parenteral MTX. Additionally, the classification of MTX as a hazardous drug by the US Department of Labor, Occupational Safety & Health Administration Hazard Communication Standard necessitates burdensome regulatory requirements of all individuals involved in its use, including formal training, the use of protective gloves and safety glasses, and monitoring for biological effects [21]. Together these issues may contribute to the low use of parenteral MTX among patients with RA in the USA.

Advantages of autoinjector technology

Prefilled autoinjector (AI) technology is one approach that can be utilized to reduce the limitations of manual injections. AIs enable patients to self-administer prescribed premeasured doses of drugs parenterally, and AIs have been successfully adopted for the delivery of a variety of drugs, including epinephrine, interferon-β and various antitumor necrosis factor therapies [22–25]. Compared with manual injections, a major advantage of AIs is the eliminated need for patients to measure injection volumes from a vial, which may improve both safety and treatment accuracy. Techniques that minimize patient contact with the needle, such as safety shields and automatic needle retraction, may also improve safety and patient anxiety concerning the handling of needles [26]. Furthermore, the improved ease of use of AIs may promote independent self-administration, thereby reducing the need for caregiver assistance or office-based treatment.

Several AIs have been approved for the delivery of biological therapies among patients with RA [22,23,27], suggesting that AI technology carries particular value for parenteral drug administration within this patient population. Preference studies have shown that AIs are preferred over manual injections, both among patients with RA and healthy volunteers [28,29]. Importantly, this preference may increase treatment adherence [30], thereby improving patient outcomes.

Introduction to the device

Development

Antares Pharma Inc. (previously Medi-Ject Corporation) has been involved in designing and manufacturing drug delivery systems for more than 40 years and has recently developed a patented MTX autoinjector (MTXAI) (Otrexup™, Antares Pharma Inc., Ewing, NJ) from their unique Vibex® platform. This technology capitalizes on company expertise in 'pressure delivery' of parenteral products, which began with early needle-free drug delivery devices. These devices combined high pressure with small delivery openings to produce a 'liquid needle' capable of penetrating skin. While some needle-free devices are still in use today [31], design knowledge and manufacturing techniques have also been translated to present-day needle-based pressure delivery AIs. These AIs incorporate mechanisms for the minimization of pain and the management of high-powered springs or high-pressure drug chambers, which allow for high-velocity drug streams utilizing standard small-diameter needles.

The MTXAI is a disposable, spring-loaded, syringe needle introducer, designed to administer a single dose of MTX in a sterile, preservative-free, unbuffered solution from a prefilled syringe contained in the device (Figure 1). The nonsterile device accommodates a prefilled 1 ml Schott or Becton Dickinson Hypak syringe and does not come into contact with the sterile contents of the syringe during the injection process. A small-diameter needle is used to penetrate skin and high pressure (thought to be up to 1000 psi) is generated by a spring-powered ram in order to expel drug into the subcutaneous dermal layer. Compared with needle-free injectors, the MTXAI is relatively simple to administer, and the use of a prefilled syringe contained in the device eliminates the need

for patients to handle vials, needles and syringes, and to measure injection doses. The device is recommended for self-administration into either the patient's thigh or abdomen and is currently available in four of the most commonly prescribed weekly doses of MTX: 10, 15, 20 and 25 mg [32].

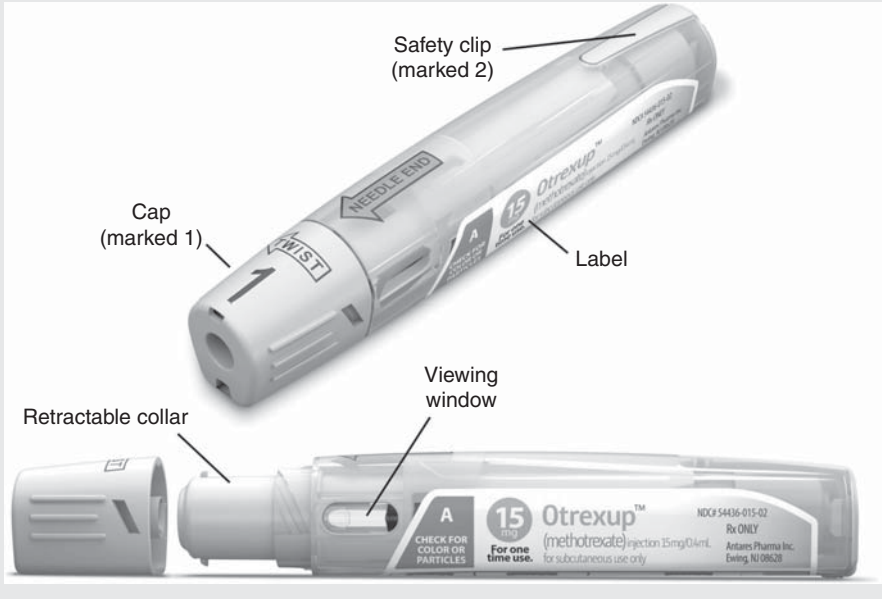

Figure 1. The Otrexup device.

Design & administration

The design and administration process of the MTXAI has been tailored to maximize safety and ease of use among patients with RA and to minimize pain. The device is D-shaped and approximately 1 inch in width, which allows for a natural fit in the palm of the patient's hand, and is large enough to grip easily [Antares Pharma Inc., Data On File]. The MTXAI is easy to self-administer; patients must first remove the safety cap, which easily strips the sterile needle shield from the prefilled syringe, then remove the safety clip, which readies the device for injection, and finally press the device's collar firmly against the injection site (thigh or abdomen), at a roughly 90° angle. This causes the collar to retract and expose the needle, which is then manually self-inserted into the skin (Figure 2). Retraction of the collar to a prespecified depth automatically triggers the device to expel the 0.4 ml dose of MTX subcutaneously. As the device is removed from the injection site, the collar automatically locks over the needle to prevent accidental needle injury. After self-administration, patients can verify that the medication was injected by checking the viewing window, which should appear blocked.

An important feature of this administration process is the method of collar activation, which accommodates patients with dexterity limitations in two important ways: first, patients do not need to press a button with their thumb to initiate injection, and second, the device collar causes the skin underneath to form a dome-like shape, eliminating the need to pinch a fold of skin around the injection site. Additionally, self-insertion of the needle is user-controlled and may be gentler than many autoinsert methods that use spring power to forcefully advance the needle through the patient's skin. The action of the MTXAI design is also rapid; the injection is completed within 1 sec [Antares Pharma Inc., Data On File], and patients are instructed to wait for a total of 3 s to ensure that the full dose was administered. This short delivery time may help to reduce injection pain, thereby increasing the likelihood of adherence and accurate dose delivery. Many formative human factor usability studies have found that patients remove AIs prior to completion of the injection stroke [Antares Pharma Inc., Data On File], and therefore, a rapid injection is essential to ensuring that a full-dose volume is delivered. The use of a small-diameter needle (27 gauge) and a shallow insertion depth (<5 mm) also help to reduce injection pain by decreasing the probability of striking a nerve.

Requirements for the storage and disposal of the MTXAI are minimal; the device can conveniently be stored at room temperature, when shielded from light. To facilitate the safe and convenient disposal of used MTXAIs, Antares Pharma has created a safe disposal program, which is provided to patients free of charge. Participating patients receive sharps containers, which they return for incineration every 6 months via prepaid packages. The program eliminates the need for patients to manage the disposal of used needles in compliance with state requirements for sharps disposal and may further improve the convenience of treatment with the MTXAI.

Currently, Otrexup is the only MTXAI approved by the US FDA and is indicated for the management of patients with severe, active RA who are intolerant of or had an inadequate response to first-line therapy [32]. Additional indications include the management of patients with polyarticular juvenile idiopathic arthritis who are intolerant of or had an inadequate response to first-line therapy, and symptomatic control of severe, recalcitrant, disabling psoriasis in adults who are not adequately responsive to other forms of therapy. Because syringe introducers are classified by the FDA as class II medical devices, a 510(k) would only be needed if the AI was marketed as a stand-alone device; as this syringe introducer is marketed together with the prefilled MTX syringe, it is considered a component of a combination product that was approved under a New Drug Application.

Clinical profile

The bioavailability, ease of use and injection pain associated with the MTXAI were investigated in two Phase II studies, each involving adult patients with RA who had been receiving

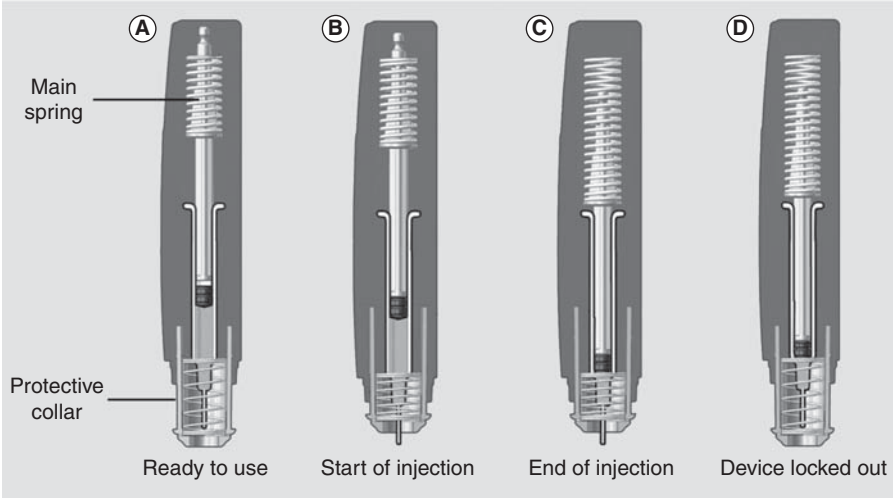

Figure 2. Stages of drug delivery. (A) Prior to use, the needle is shielded by a protective collar. **(B)** The collar retracts as it is pressed against the skin, thereby exposing the needle for manual insertion. **(C)** Retraction of the collar automatically triggers the main spring to release, thereby injecting the contents of the prefilled syringe. **(D)** As the device is removed from the skin, the collar returns to its position covering the needle.

MTX for at least 3 months. Each patient in these studies was assigned an MTX dose among the four available MTXAI doses (10, 15, 20 and 25 mg) by the treating physician, based on the patient's current MTX treatment and disease control.

Actual human use study

The injection pain and ease of use of the MTXAI were investigated in a Phase II, multicenter, open-label, single-dose, single-arm, in-clinic US study of 101 adults with RA [33]. Each patient successfully performed self-administration after being trained on the proper use of the MTXAI by nursing staff at the investigator sites and evaluated pain associated with self-administration on a 100-mm visual analog scale (0 indicates no pain and 100 indicates the worst pain imaginable). Patient-reported administration site pain was minimal, with overall median visual analog scale pain scores of 1 immediately after self-administration, and 0 the following day (Table 1). Rates of injection-site erythema, or redness, were also low; the most severe erythema reported was very slight or barely perceptible, and occurred in 7.7% of patients (Figure 3). This study additionally demonstrated the lack of difficulties associated with self-administration as more than 90% of patients agreed or strongly agreed that the 'device was easy to use' (Figure 4).

Table 1. Administration site pain (100-mm visual analog scale).

Administration site pain	Methotrexate				
	10 mg (n = 20)	*15 mg (n = 30)*	*20 mg (n = 31)*	*25 mg (n = 20)*	*Overall (N = 101)*
Day 1					
Mean (SD)	1.0 (1.0)[†]	7.6 (15.6)	2.2 (2.9)	2.4 (2.6)[†]	3.6 (9.1)[‡]
Median	1	2	1	2	1
Day 2					
Mean (SD)	1.7 (4.5)	2.0 (4.1)	1.0 (1.6)	1.0 (1.2)	1.4 (3.2)
Median	0	0	0	0.5	0

[†]n = 19.
[‡]n = 99.
VAS: Visual analog scale (0 = no pain and 100 = worst pain imaginable).

Bioavailability study

The bioavailability of MTX as delivered by the MTXAI was compared with that delivered by oral MTX in a multicenter, open-label, randomized, three-way crossover, Phase II study [8]. Each patient in the study received a random sequence of three MTX treatments delivered 1:1:1 as oral MTX, MTXAI self-administered to the thigh and MTXAI self-administered to the abdomen. Overall, 49 patients participated and received one or more doses of study drug. Blood samples were obtained for pharmacokinetic analysis predose and at multiple time points throughout 24 h after administration. Pharmacokinetic analysis demonstrated a bioequivalence between MTXAI self-administered to the thigh compared with the abdomen, suggesting that these two injection sites allow for equivalent drug delivery [8]. Furthermore, systemic bioavailability following MTXAI self-administration was shown to increase dose-proportionately, indicating no absorption limitations within this range (Figure 5). In contrast, the bioavailability of MTX delivered orally reached a plateau at approximately 15 mg, likely as a result of GI absorption limitations [9,10].

Safety

The safety of the MTXAI was also assessed in each of these studies, and no unexpected treatment-emergent adverse events (TEAEs) were identified, based on the known safety profile of MTX. Within the actual human use study, three patients (2.97%) experienced one or more TEAEs; of these, one was considered by the investigator to be related to study drug (mild headache in a patient receiving 20 mg MTXAI) [33]. Within the bioavailability study, five patients (10.2%) experienced one or more TEAEs; of these, one was considered by the investigator to be related to study drug (mild and transient nausea in a patient receiving oral MTX) [8].

Alternative injection devices used in the treatment of RA

Otrexup is the only MTX delivery device approved by the FDA, although several other injection devices have been approved for the delivery of biological therapies to patients with RA (Table 2) [22,23,27]. Many of these devices have been designed with similar characteristics to the MTXAI, although additional unique attributes of the MTXAI may make this device particularly well suited to the specific needs of the RA patient population.

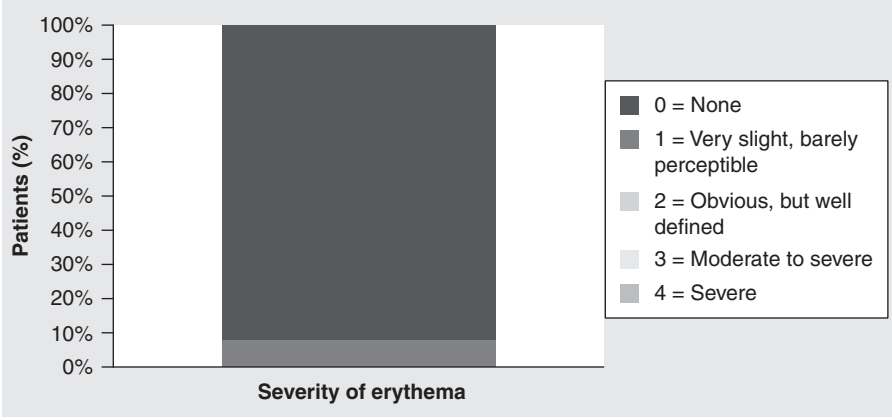

Figure 3. Severity of erythema.

The MTXAI is one of four FDA-approved injection devices indicated for the treatment of RA, including a total of three AIs [22,23,32], and one pen injector [27]. Additionally, seven prefilled syringes [22,23,27,34–37] are available. Although some patients continue to use prefilled syringes, a major advancement of AI and pen injector technology is the automated injection step, which eliminates the requirement for patients to use their thumb to manually depress a syringe plunger. This advancement may increase the safety and ease of use of the device, particularly among patients with functional limitations. Additionally, the use of a protective collar, which surrounds the needle within AIs and pen injectors, decreases the risk of accidental needle injury and may reduce anxiety among patients fearful of needles. The force of the protective collar against the skin surrounding the injection site may also distract or desensitize patients to the needle insertion and decrease the perception of pain.

Among the AIs used in the treatment of RA, the MTXAI is unique, primarily because of its self-inserted needle mechanism and its collar-activated injection mechanism (Figure 2). Unlike other AIs, the insertion of the needle into the skin is controlled by the user, which can be gentler than spring-powered autoinsertion methods. Additionally, the injection step is automatically initiated by retraction of the safety collar rather than the press of a button, which minimizes the physical requirements associated with injection. Another important advantage of the MTXAI is its rapid drug delivery; during the injection step, users are instructed to hold the device in place for 3 s [Antares Pharma Inc., Data On File], unlike the 10–15 s required for biological AIs [22,23,27]. The rapid speed of injection may promote safety, ease of use and treatment adherence as users are less likely to prematurely remove the device from the injection site. Additional benefits of the MTXAI involve its drug formulation; the MTXAI, unlike the biological AIs, does not require refrigeration and can be delivered as a relatively small volume (0.4 vs 0.5–1 ml).

Conclusion

The MTXAI fulfills an unmet medical need among patients with RA by facilitating the safe and convenient parenteral administration of MTX. Because of an increasing awareness among rheumatologists regarding the value of parenteral MTX, as well as the technological advancements of the MTXAI specific to the needs of patients with RA, the MTXAI may become a valuable MTX delivery method and may increase the usage of parenteral MTX as a treatment option for RA.

An important benefit of increased parenteral MTX usage is the potential for greater numbers of patients to reach an optimally effective MTX dose. Because of the greater systemic exposure provided by parenteral MTX, parenteral administration may extend the therapeutic range of MTX and benefit patients who would otherwise discontinue MTX due to intolerance or inadequate efficacy. Importantly, exposure optimization may improve patient outcomes and increase rates of remission and low-disease activity. Another benefit of increasing MTX response rates is a diminished need for additional therapies such as nonsteroidal anti-inflammatory drugs, prednisone and

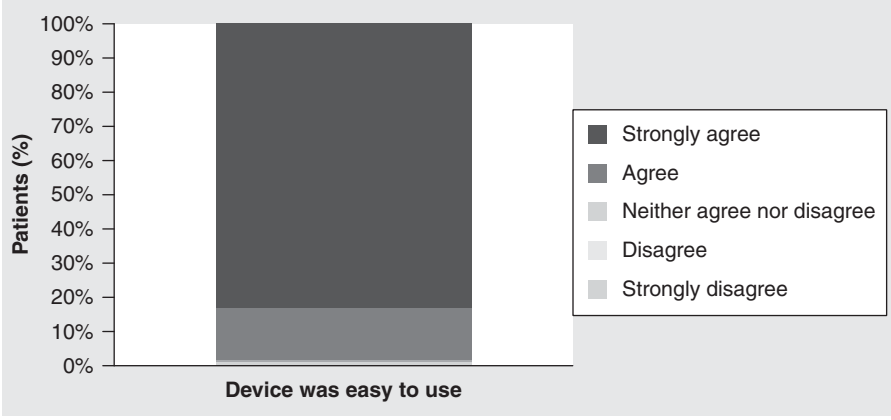

Figure 4. Patient ratings of Otrexup.

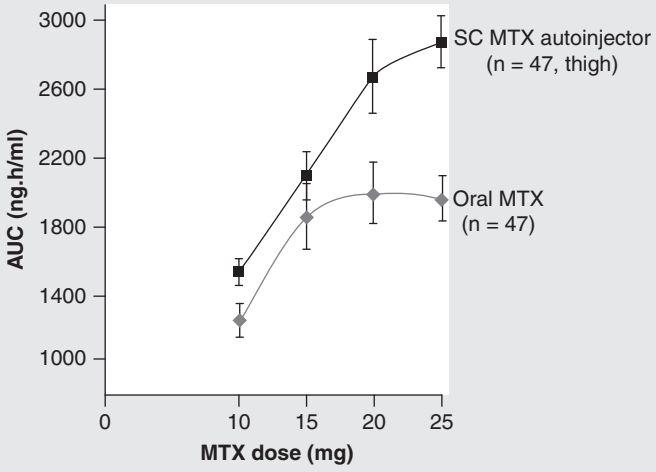

Figure 5. MTX bioavailability.
AUC: Area under the curve; MTX: Methotrexate; SC: Subcutaneous.
Reproduced with permission from BMJ publishing group.
Data taken from [8].

biologics. The ability to delay the initiation of biological therapies may be particularly important because of concerns regarding both the safety and cost associated with the use of biologics [38,39].

Although not all patients with RA will require parenteral MTX administration or benefit from AI technology, the MTXAI device fills a specific therapeutic need and is uniquely tailored to the needs of this patient population. The MTXAI provides a new treatment option for patients with RA and may be a valuable tool for clinicians to consider throughout their patients' course of treatment.

Expert commentary

The most important specifications of the MTXAI contribute to its safety and ease of use among patients with RA. The incorporation of a protective collar surrounding the needle and the minimal handling requirements of the MTXAI decrease the potential for injury, and the shallow insertion depth, narrow needle thickness and self-insertion method minimize injection-site pain. Furthermore, the size of the device, its rapid speed of injection and the eliminated need for users to measure injection volumes or manually initiate the injection stroke contribute to the convenience of the MTXAI, particularly among patients with RA who may experience limitations in manual dexterity.

The widespread usage of MTX among patients with RA and its potential to be administered regularly over several years or more suggest that the MTXAI may be an appropriate treatment option for a large number of patients with RA. Additionally, the ability of MTX to be combined with other conventional or biological DMARDs suggests that the MTXAI could be used concomitantly with various other RA treatments. Future developments could further increase the convenience of treatment by combining AI device technologies so that MTX and other parenteral therapies could be combined into a single weekly injection. Improvements in treatment convenience could be expected to increase treatment adherence and may have important effects on patient outcomes.

Five-year view

Because of the long history of MTX as a safe and effective treatment for RA, as well as its widespread usage within the

Table 2. Alternative injection devices approved by the FDA for rheumatoid arthritis.

Device characteristics	Simponi [23] (Janssen Biotech)	Enbrel [22,40] (Amgen)	Humira [27] (AbbVie)	Otrexup [32] (Antares)
Type of device	Autoinjector (SmartJect)	Autoinjector (SureClick)	Pen injector	Autoinjector
Drug	Golimumab	Etanercept	Adalimumab	Methotrexate
Insertion mechanism†	Autoinserted	Autoinserted	Autoinserted	Self-inserted
Injection mechanism	Button activated	Button activated	Button activated	Collar activated
Doses available	50 mg in 0.5 ml 100 mg in 1 ml	50 mg in 0.98 ml	40 mg in 0.8 ml	10 mg in 0.4 ml 15 mg in 0.4 ml 20 mg in 0.4 ml 25 mg in 0.4 ml
Needle gauge	27	27	27	27
Injection indicator‡	Yellow indicator in viewing window	Purple indicator in viewing window	Yellow indicator in viewing window	Blocked viewing window
Length of injection	Up to 15 s	15 s	10 s	3 s
Storage temperature	Refrigeration	Refrigeration	Refrigeration	Room temperature

†Self-insertion (manual insertion of the needle into the skin) vs autoinsertion (automatic spring-powered insertion of the needle into the skin).
‡An indication that the injection is complete.
RA: Rheumatoid arthritis.

RA patient population, MTX will likely continue to be an integral component of RA treatment throughout the next 5 years or more. Additionally, we expect its critical role within first-line therapy, including recommendations by both the American College of Rheumatology and the European League Against Rheumatism [3,4], to remain unchallenged.

Within the next several years, the use of MTX among patients with RA in the USA may increase because of increased access to care following implementation of the Affordable Care Act and earlier referrals from primary care physicians to rheumatologists. Starting and maximum MTX doses prescribed by rheumatologists may also increase because of a greater understanding of the pharmacokinetics of oral and parenteral MTX and the continued availability of the MTXAI. A greater use of electronic medical records may further improve MTX dose optimization, thereby increasing the numbers of patients who can benefit from treatment with MTX.

The availability of the MTXAI is likely to further facilitate these trends by increasing the accessibility of parenteral MTX and by enabling patients to achieve higher maximum MTX doses. Because of its convenience and ease of use, the MTXAI is likely to appeal to many patients with RA and may become established as a valuable treatment option within the RA patient population.

Information resources

- Arthritis Foundation. www.arthritis.org
- American College of Rheumatology. www.rheumatology.org
- Otrexup™. www.otrexup.com
- Otrexup prescribing information. (Antares Pharma, Inc., 2013, Ewing, NJ, USA). www.otrexup.com
- Simponi® Medication Guide (Janssen Biotech, Inc., 2013, Horsham, PA, USA). www.simponi.com
- Enbrel® Instructions for Use (Amgen, 2013, Thousand Oaks, CA, USA). www.enbrel.com
- Humira® Instructions for Use (AbbVie Inc., 2013, North Chicago, IL, USA) www.humira.com

Financial & competing interests disclosure

M Schiff is a consultant for Antares Pharma; J Jaffe is an employee of Antares Pharma; B Freundlich is an employee of Antares Pharma, a shareholder of Pfizer, and a consultant for Celgene and Bristol-Myers Squibb; P Madsen is an employee of Antares Pharma. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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Key issues

- Methotrexate (MTX) is the cornerstone of treatment for patients with rheumatoid arthritis (RA) because of its efficacy and safety, and it is typically administered orally in the USA.
- Although oral MTX is generally well tolerated, the primary reasons for its discontinuation are gastrointestinal (GI) distress and inefficacy.
- Switching to parenteral MTX may offer improved GI tolerability and systemic exposure, and may be an underutilized treatment option for patients who experience an inadequate response to oral MTX at their greatest tolerated dose.
- Patients appear to frequently avoid parenteral drug administration because of difficulties in safely administering an accurate dose; these difficulties may be exacerbated within an RA patient population because of functional limitations.
- A safe and easy method of parenteral MTX administration may improve treatment adherence and patient outcomes and expand the clinical utility of MTX as a treatment option for RA.
- Otrexup™ is the only automated MTX injection device currently approved by the Food and Drug Administration and allows patients to self-administer prespecified doses of MTX subcutaneously.
- Otrexup may improve upon standard subcutaneous injections requiring a vial, needle and syringe by eliminating the need for patients to measure doses and manually depress a syringe plunger.
- Otrexup may improve upon other autoinjectors indicated for the treatment of RA by allowing for self-controlled manual insertion of the needle, a button-less automatic injection mechanism and a rapid injection stroke.
- Self-administration of MTX via autoinjection delivers greater systemic levels of MTX than oral administration of an equivalent dose and is associated with minimal patient-reported pain.
- MTX autoinjection may be a valuable tool to facilitate the safe and accurate administration of parenteral MTX among patients with RA.

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•• of considerable interest

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