


Potential Benefits of the Self-Administration of Subcutaneous Methotrexate with Autoinjector Devices for Patients: A Review

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Abstract: The role of patient adherence in improving the efficacy of any treatment is widely accepted, as well as its impact in optimizing the use of healthcare resources and associated costs. Adherence is particularly affected in chronic conditions, such as rheumatoid arthritis (RA), requiring long-term therapies and a commitment of the patient to manage his/her disease. Methotrexate (MTX) is one of the mainstays of treatment for several immune-mediated inflammatory joint and skin diseases, especially RA. The use of parenteral MTX, particularly when administered as a subcutaneous (SC) injection, has recently raised a great interest to overcome the limitations of oral MTX. For addressing this issue, new optimized self-injection systems have been developed to improve the ease of use of SC MTX. Increasing evidence shows how patients tend to opt for autoinjectors over prefilled syringes or conventional syringes in terms of easiness of use, preference and satisfaction, regardless of whether the treatment is a biologic or MTX. Additionally, positive views and beliefs of patients about treatment may contribute to increasing expectations of effectiveness and treatment adherence. Similarly, the implementation of prefilled pens in clinical practice might be a way to facilitate and simplify the self-injection of SC MTX delivery, optimizing adherence and treatment outcomes as a consequence. This article aimed to review the available literature data on the use of MTX autoinjectors and their impact on treatment adherence and patients' perceptions.

Keywords: adherence, rheumatoid arthritis, methotrexate, autoinjector

Introduction

Therapeutic efficacy depends on the quality of a drug, its bioavailability and medication adherence. Medication nonadherence for chronic conditions remains a challenge to contemporary medicine. The World Health Organization (WHO) claimed in 2003 that improving patient adherence to long-term therapies would be as beneficial as any biomedical progress. Consequently, patients' adherence to treatment has become a major requirement for improving chronic disease control and optimizing the use of healthcare resources and costs.¹⁻⁴ Rheumatoid arthritis (RA) is a chronic systemic autoimmune inflammatory disease with a prevalence of around 1% in developed countries.^{5,6} The inadequate control of the RA may lead to accumulating joint damage, irreversible disability, poorer quality of life (QoL) and higher mortality.^{7,8} Therefore, efforts addressed to gain knowledge of the factors causing poor adherence will lead to better outcomes. Reasons for poor adherence may be related to disease, treatment, provider, the health system and the patient.

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Patients' needs are specific to their situation, hence the need to better understand the relationship between patients' perceptions of the need for a given treatment if we want to improve medication adherence. In short, a therapy framework should meet patient circumstances for optimal efficacy and more effective use of healthcare resources.^{1-4,9-11} Treatment adherence in RA has been extensively investigated and reviewed in several meta-analyses¹²⁻¹⁵ that show suboptimal compliance, especially to the reference therapy methotrexate (MTX). The subcutaneous (SC) formulation of MTX, unlike the oral delivery, is the best option in pursuing a higher efficacy and better tolerability; but while the route of administration does not appear to influence drug adherence in RA,^{14,16-22} some difficulties associated with syringe use may difficult the use of the SC delivery. Therefore, to avoid the problems in administering self-injections using the classic syringes from reduced manual dexterity patients with RA, new drug-delivery devices have been developed that facilitate the use and reduce the discomfort. Although the evidence is not robust, optimizing the SC self-administration of MTX could have the potential to improve adherence.

This narrative review is based on the following premises: 1) patient's perceptions about medication play an important role in adherence and, in consequence, in clinical outcomes and medical costs of chronic diseases such as RA; 2) the SC MTX has gained attention among rheumatologists during the last years, and devices for self-injection have increased as an alternative to classic syringes; 3) these new marketed devices have shown a high level of usability, acceptance, and satisfaction that may lead to enhance the clinical outcomes. Thus, we aim to discuss the role of the autoinjector devices in adherence and whether their implementation in clinical practice improves therapy outcomes.

Materials and Methods

We conducted a narrative review of the literature using the following methodology. The literature search strategy was focused on the following question using the PICO framework:²³

"How does the use of pens/autoinjectors versus others forms of injection affect medication adherence and perceptions of patients with RA receiving long-term therapies? (where the "Participants" are the "patients with RA" and those receiving "long-term therapies," the "Intervention" is "the use of pens/autoinjectors," the "Comparator" is

"other forms of injection?" and the "Outcome" is "medication adherence and patient perceptions")".

Citations were limited to those from indexed journals, communications from international meetings, and government entity guidelines (eg, WHO). Studies also had to be published in English within the last 15 years. Any article outside of our focus of interest, ie, any publication that did not answer the question we were asking was excluded.

Literature search was conducted through the PubMed and Google Scholar databases, using combined Medical Subject Headings (MeSH) and free-text terms related to "methotrexate", "rheumatoid arthritis", "chronic disease", "long-term treatment/therapy", "lifespan treatment/adherence", "disease-modifying antirheumatic drugs (DMARDs)" "adherence", "compliance", "persistence", "preference", "ease of use", "satisfaction", "pen", "auto-injector", "prefilled", "syringe".

We perform two rounds of searching (Figure 1). In the first round, we extracted 84 citations, from which 13 were discarded after reviewing the title and abstract and confirming that the topic was not related to the purpose of this review. In the second round, 13 citations were excluded for not fulfilling the inclusion criteria. Finally, we selected 58 citations that responded more accurately to our question. Furthermore, studies were ranked by scientific evidence level. Thus, preference was given to systematic reviews and meta-analysis over narrative reviews and to guidelines from government entities over authors' opinions; in the latter case, the opinion of committees was preferred over a single author's opinion.

Results

Overview of Patient Medication Adherence Concept and Measures

Adherence is defined as "the extent to which a patient acts per the prescribed interval and dose of a dosing regimen".²⁴ Adherence is usually reported as the percentage of the prescribed doses of medication taken by the patient over a specific period, although in retrospective studies, the concept of medication possession ratio (MPR) is often employed.²⁴ The term compliance, sometimes wrongly referred to as adherence, implies patient obedience in following the prescriber's recommendations. A type of non-adherence is called non-persistence, which describes the percentage of patients who decide not to continue taking the medication without medical advice.

In short, the concept and measure of adherence are as complex and variable as factors affecting it which range from patient expectations and attitudes, and disease characteristics,

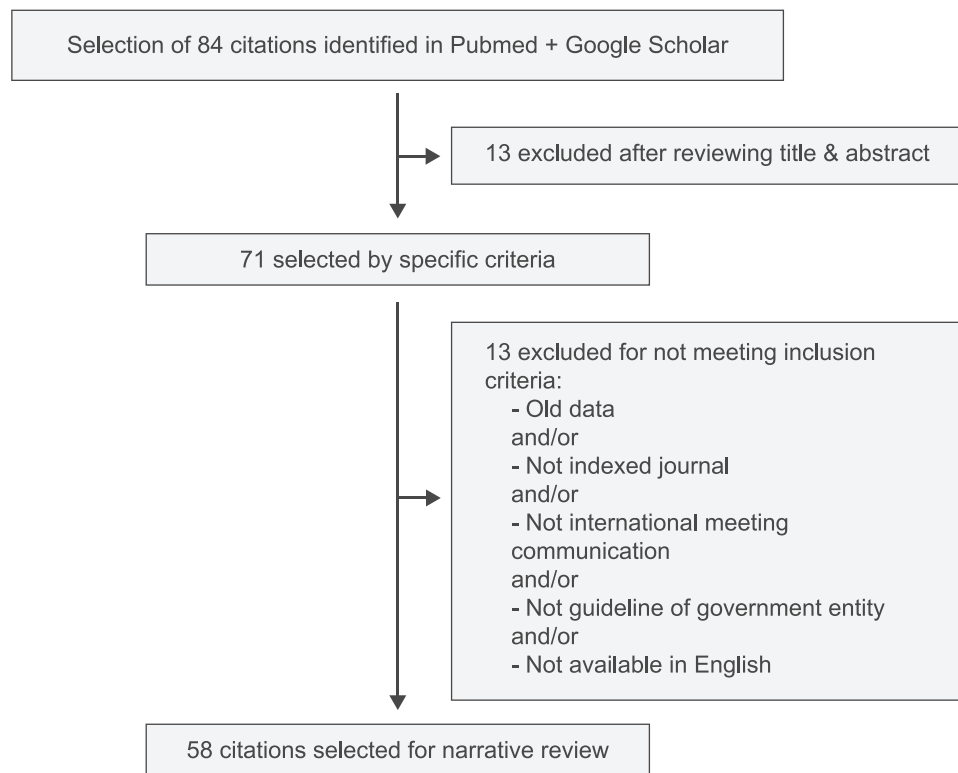


Figure 1 Literature search workflow diagram. From the initially identified citations, they were finally selected 58 meeting the inclusion criteria and responded to the following question using the PICO framework: "How does the use of pens/autoinjectors versus other forms of injection affect medication adherence and perceptions of patients with RA receiving long-term therapies".

to convenience, cost, route of administration, adverse events, and practitioner support.²⁵ If focused on RA several studies have also shown different estimates of MTX adherence because of the heterogeneity in the assessment methods.¹² For instance, MPR, the Compliance Questionnaire Rheumatology (CQR), the Visual Analogue Scale (VAS), the Medication Event Monitoring System (MEMS), drug record registry, claims data, and the Medication Adherence Report Scale (MARS-5)^{12,13,15} have been used throwing a variety of results that do not allow to build a clear pattern of factors that influence adherence and persistence.

Methotrexate in Rheumatoid Arthritis Management: The Importance of Subcutaneous Administration and the Influence of the Route of Administration

MTX is a mainstay in the therapy of RA.^{26,27} However, evidence indicates high variability in terms of efficacy and safety outcomes that can be ascribed, at least in part, to the individual's pharmacogenomic profile. The saturable intestinal absorption of oral MTX limits its bioavailability and efficacy²⁶ while SC administration results in rapid and

complete absorption, higher serum levels, and less variable exposure. In some cases, the use of parenteral route should be considered to overcome the limitations of oral administration of MTX. A recent article by Tornero Molina et al,¹⁶ for the use of parenteral MTX in rheumatic diseases, mainly RA, and based on best evidence and experience in order to solve frequent questions and help in decision-making strategies, indicated that patients with an inadequate response to oral MTX (15 mg/week), escalating the dose utilizing the parenteral route is clinically more effective. The use of parenteral MTX is recommended to be also considered in patients with highly active disease, poor adherence to oral treatment, taking multiple drugs, or obesity.¹⁶

Additionally, considering the expert consensus document by Tornero-Molina et al, in RA patient's refractory or intolerant to oral MTX and even poor-adherents, the switch to SC MTX is recommended before introducing a biologic agent.¹⁷ The assessment of effectiveness and safety of SC MTX has been mainly focused on RA and evidence highlights the superior clinical efficacy of SC MTX over oral MTX.²⁶ Moreover, the higher drug exposure resulting from SC administration does not entail

a higher risk of gastrointestinal adverse events or increased safety issues.

A multicenter, randomized, double-blind trial comparing the efficacy and safety of oral and SC MTX in patients with active RA found that SC administration was significantly more effective than oral administration with no differences in tolerability.²⁰ This fact has also been described in a prospective study even without an increase in adverse effects.²⁸ Another study in a prospective cohort of patients with early RA concluded that initial SC MTX was associated with lower rates of treatment failures and greater clinical efficacy than oral MTX, with no difference in toxicity taking into account the expected difference in MTX bioavailability when SC MTX is administered compared to oral MTX at higher doses.²⁶ A short-term study demonstrated that oral split doses of MTX are better than an oral single dose and similar to parenteral MTX in terms of efficacy.²⁹ However, MTX given orally shows a lower absorption and a worse safety profile regarding gastrointestinal toxicity that may justify the switch to SC MTX instead to biologics.^{16–20,22,27}

Likewise, as we have previously mentioned, based on the expert consensus document by Tornero-Molina et al., and should being re-evaluated periodically, in situations where initial doses are necessary as in overweight patients, the switch from oral MTX to SC MTX is also recommended.¹⁷ In support of this, evidence has demonstrated that SC MTX both as initial therapy in naive patients^{20,26} or subsequent therapy in non-responder patients improves treatment persistence, and clinical efficacy mainly due to its favorable bioavailability,³⁰ and optimizes the use of healthcare resources.²⁷ Notably, a recent subanalysis of the RA Excellence project in Spain showed that MTX escalation to full doses is not done with adequate speed and that the subcutaneous route is used in a small proportion of patients in clinical practice (only 12% of patients changed the route of administration).³¹ Similarly, the study Symphony Health Solutions covering 274 million patients in the US showed that only 16% of patients were changed from oral to SC MTX.¹⁸ That is, real-world evidence is highlighting the underuse of SC MTX after failure to oral administration, despite the recommendation that RA patients need to have tried and failed both oral and SC MTX before assuming a complete failure or intolerance to MTX and start biologics administration. This recommendation has been adopted considering the evidence that SC administration ensures

higher plasma concentration and drug bioavailability, and thus greater clinical efficacy.^{19,20,32} There is even evidence that the use of SC MTX after oral delays the onset of biological therapy. The MENTOR study, for example, provided evidence for the effectiveness and enhanced tolerability of SC MTX in prolonging disease control in patients who have failed oral MTX without necessarily the need to introduce alternative DMARD or biologic therapy.³³ Several studies have proposed that SC MTX has an important role to play in the long-term management of patients with RA from higher-cost treatment pathways to lower-cost treatment pathways. It can be also self-administered at home, providing an improvement in patient satisfaction.^{34,35} Taylor et al., provided an evidence-based discussion as to how to achieve the best outcomes with MTX in the management of RA highlighting that the parenteral administration of MTX has the advantages of maximising bioavailability, reducing gastrointestinal intolerance, and potentially enhancing compliance and adherence being highly cost-effective.³⁶ Based on the 2016 European League Against Rheumatism (EULAR) recommendations from 2016, MTX should be part of the first treatment strategy with csDMARDs, except in patients with contraindication and in case of non-response, change to another csDMARD as a strategy before adding a biological.²¹

MTX remains the initial drug of choice for treating RA, both as monotherapy and in combination with other RA drugs,²¹ and the SC route is the best alternative to achieve better clinical outcomes; however, the evidence available about the effect of using the SC formulation to improve adherence is not so conclusive. While several studies demonstrated improved treatment continuation associated with SC MTX over the first year of treatment compared to oral administration,²⁶ others found improved persistence either in patients initially treated with SC MTX or those switched from oral to SC administration³⁰ similar adherence regardless of the route of administration,¹⁴ or MTX adherence highly variable because of different populations, follow-up durations, adherence definitions or assessment methods.¹² Added to this is the difficulty that many patients may have in self-medicating, or the pain, anxiety, discomfort, and syringe fear they may experience, which, although do not contribute directly to increase adherence, is affecting the convenience of treatment and patient motivation.

Pen Devices and Autoinjectors for Drug Parenteral Administration

The long-term goal of RA medications is to slow or stop the disease process, particularly joint damage, so patients can preserve their autonomy and QoL. Optimizing forms of administration is likely to facilitate the treatment compliance and commitment that chronic treatments require.

For some patients, RA therapies need to be injected. However, they may have difficulties in manipulating syringes as a result of the functional impairment of the disease and the hand small joint involvement impairing dexterity.

Additionally, evidence supports that many patients with RA show difficulty in adhering to their medication, and that patient preferences and motivations positively affect adherence since it facilitates the acceptance of the issues surrounding medication for chronic disease.^{1–4,11} A recent systematic of patients' perspectives on the SC route of administration²² demonstrates the importance of the distinct methods and routes of administration on patient choice for the management of chronic disorders (diabetes, growth hormone deficiency, migraine, multiple sclerosis, and RA). These studies concluded that pen devices and autoinjectors are preferred to deliveries via needle or syringes in terms of convenience and portability.²² Table 1 presents the publications reviewed which deal with the use of self-injection devices for different chronic conditions and long-term therapies. Adherence to diabetic medication has been widely studied together with patient preferences and other perceptions.^{37–39} These studies found better outcomes with pen usage and a positive effect of the utilization of such devices. Furthermore, a narrative²⁵ and systematic review⁴⁰ compiled information on adherence/perceptions from type 2 diabetes mellitus (DM2) patients using pen devices for insulin administration. Conclusions advocated simplifying treatment regimens and caring patient motivation and education among the interventions to optimize adherence,²⁵ which positively correlates with the use of pen devices.⁴⁰ In patients with inflammatory bowel disease, compliance with biologic therapy is favorable with more than three-quarters of patients who adhere to their anti-TNF therapy.⁴¹ For instance, a study in patients with ulcerative colitis showed that the majority preferred self-administration with golimumab autoinjector over a prefilled syringe.⁴² In multiple sclerosis, the adherence to medication has been focused on interferon beta-1a SC devices. The ATTAIN and REDEFINE studies reported a preference for once-weekly autoinjectors over prefilled syringed among patients.⁴³

It would be hypothesized that the characteristics of the disease may impact perceptions of devices. To address this hypothesis, a study to assess the performance, safety, subject acceptance and compliance of a disposable autoinjector for SC injections of MTX in healthy volunteers was performed, comparing SC injections performed by subjects using the autoinjector with SC injections performed by nurses using a syringe.⁴⁴ No differences were found in terms of safety or performance between the two delivery ways but better outcomes were obtained in terms of pain, preference, and acceptance when the drug was self-administered.⁴⁴

Several studies have demonstrated that self-injection versus injection by health care workers can increase patient treatment adherence and, consequently, reduce costs by decreasing the frequency of hospital visits, which benefits patients in terms of cost, time, ease of use, improved self-esteem, and greater independence in their social, domestic, and professional lives.^{45,46}

RA is a good example of how the limitations related to the severity of disease and progression may affect medication adherence by complicating the procedure of self-autoinjection. A study in RA patients⁴⁷ showed a high level of patient acceptance of an autoinjector developed for facilitating the SC self-injection, which had been successfully tested in healthy volunteers⁴⁴ and patients with multiple sclerosis.⁴⁸ Notably, usability and compliance were successful in patients with severe hand disability.⁴⁷ The findings of this study add to the evidence supporting the use of autoinjectors to help improve treatment compliance among patients with chronic diseases.

Results from several studies have shown that patients with RA favor treatment devices that are easy to use, convenient, less painful and take less time to use, and patients have demonstrated a preference for autoinjector devices over more conventional methods of treatment administration,^{48–53} such as syringes.

The TOUCH study,⁴⁹ which evaluated two self-administration devices for adalimumab, a prefilled syringe and an autoinjection pen, showed how patients preferred the pen versus the syringe and perceived it as easier to use and more convenient. Furthermore, a considerable proportion of patients reported that the pen was less painful to use than the syringe.

Two etanercept autoinjectors, when compared, showed different ratings of preference and acceptability that varied in function of specific attributes of the devices.⁵⁰ The abatacept pre-filled autoinjector has demonstrated to be highly acceptable.⁵¹ Patient satisfaction and confidence regarding

Table I Parenteral Self-Administration Through Pen/Autoinjectors for Long-Term Therapies and Chronic Diseases

Drug Delivered and Condition	Reference	Type of Publication	Summary
<ul style="list-style-type: none"> • Insulin • Diabetes 	Cheen et al, 2014 ³⁷	Research article	• Retrospective observational study, single center, N = 955 patients.
			• Outcome measure adherence in terms of: compliance (by MPR) & persistence.
			• Comparison of patients using prefilled pens vs those using vial/syringe.
			• Results: despite MPR was similar, prefilled pen users were more persistent.
	Ramadan et al, 2015 ³⁹	Research article	• Prospective observational study, 5 centers, N = 71 patients.
			• Primary endpoints: simplicity & safety of administration, preference & convenience of patients.
			• Comparison of patients using pens vs those using conventional vial/syringe.
	Miao et al, 2014 ³⁸	Research article	• Pen was easier to use and less painful.
			• Retrospective observational study, database, N = 7856 patients of DM2 ≥ 65 years old, insulin glargine.
			• Follow-up study outcomes: persistence and adherence (by MPR).
			• Comparison of patients using disposable pens vs those using conventional vial/syringe.
	Tiktin et al, 2016 ²⁵	Narrative review	• Results: Pen users showed greater persistence, duration of persistence and adherence.
			• Literature search aiming to identify factors affecting adherence to medications in DM2, N = 30 studies.
	Lasalvia et al, 2016 ⁴⁰	Systematic review/meta-analysis	• Authors recommend to simplify regimes, to improve provider-patient communication and to provide support and education of patients.
			• Revision to evaluate efficacy of pens vs vial/syringe, finally included N = 17 studies on DM2.
<ul style="list-style-type: none"> • Biologics anti-TNF • Autoimmune & chronic inflammatory diseases 	Lopez et al, 2013 ⁴¹	Systematic review	• Authors concluded that pen use yields clinical benefits and is positively correlated to patient adherence/preference.
			• Revision of methods of assessment, prevalence and predictors of non-adherence in inflammatory bowel diseases, finally included N = 13 studies
	Kivitz & Segurado 2007 ⁷⁰	Expert opinion	• Authors concluded >75% adhere to biologics and suggests that syringe vs pen might be a predictor for non-adherence.
			• Authors focus on adalimumab-charged HUMIRA pen (adalimumab) and the outcomes of the TOUCH study.
	Vermeire et al, 2018 ⁴²	Research article	• Authors suggests pens/autoinjectors would become the preferred choice.
			• Open-label, multicenter, randomized crossover clinical trial, N = 91 moderate-to-severe ulcerative colitis patients.
			• Assessments: preference, self-injection perceptions (ease-of-use, discomfort, overall impression), safety.
			• Comparison of golimumab prefilled syringe vs autoinjector.
			• Authors concluded patients generally prefer autoinjectors.

(Continued)

Table I (Continued).

Drug Delivered and Condition	Reference	Type of Publication	Summary
<ul style="list-style-type: none"> • IFN-β1a • Multiple sclerosis 	Seddighzadeh et al, 2014 ⁷¹	Research article	<ul style="list-style-type: none"> • Sub-study: data mining from the ATTAIN trial (extension of the ADVANCE trial: Phase III, double-blind, randomized, multi-center), N = 39 relapsing-remitting multiple sclerosis patients.
			<ul style="list-style-type: none"> • Assessments: safety, tolerability (pain by patient & clinician), patient perceptions (ease-of-use, satisfaction).
			<ul style="list-style-type: none"> • Comparison of peginterferon-beta 1a prefilled syringe vs autoinjector.
			<ul style="list-style-type: none"> • Results: similar safety & tolerability profile, patient find autoinjector easy to use and convenient.
			<ul style="list-style-type: none"> • Authors suggests autoinjector potentially would improve QoL.
	Limmroth & Gerbershagen 2014 ⁴³	Expert opinion	<ul style="list-style-type: none"> • Authors focus on single-use autoinjector for once-weekly intramuscular delivery.
			<ul style="list-style-type: none"> • Authors described a preference for the devices and suggested that they might contribute to improve adherence and QoL.
	Wray et al, 2018 ⁴⁸	Research article	<ul style="list-style-type: none"> • REDEFINE clinical trial (phase IV, randomized, multicenter, two-center, crossover study), N = 97 relapsing-remitting multiple sclerosis patients.
			<ul style="list-style-type: none"> • Assessments: patient perceptions (ease-of-use, satisfaction and QoL), compliance and safety.
			<ul style="list-style-type: none"> • Comparison of single-use autoinjector vs reusable autoinjector.
			<ul style="list-style-type: none"> • Results: both devices were perceived as easy or very easy to use.
			<ul style="list-style-type: none"> • Authors speculate having two autoinjector options may offer the potential to accommodate patient preferences.
<ul style="list-style-type: none"> • No drug • Healthy individuals 	Berteau et al, 2010 ⁴⁴	Research article	<ul style="list-style-type: none"> • Randomized, single-center, crossover study, N = 40 healthy volunteers.
			<ul style="list-style-type: none"> • Assessments: device performance, patient perceptions (preference and acceptance), compliance, safety.
			<ul style="list-style-type: none"> • Comparison of self-injections by a pen vs syringe by healthcare personnel.
			<ul style="list-style-type: none"> • Results: although both methods performed almost equally, patients prefer and has greater acceptance for autoinjector.
<ul style="list-style-type: none"> • No drug • Rheumatoid arthritis 	Schwarzenbach et al, 2014 ⁴⁷	Research article	<ul style="list-style-type: none"> • Randomized, single-center, crossover study, N = 65 RA patients.
			<ul style="list-style-type: none"> • Assessments: patient perceptions (ease/comfort of use, acceptance), usability and compliance.
			<ul style="list-style-type: none"> • Evaluation of an autoinjector regardless the treatment by performing mock injections finding a high level of patient acceptance.
			<ul style="list-style-type: none"> • Results: high acceptance and compliance.
			<ul style="list-style-type: none"> • Authors speculate use of autoinjector may improve compliance of patients with chronic diseases.

(Continued)

Table I (Continued).

Drug Delivered and Condition	Reference	Type of Publication	Summary
<ul style="list-style-type: none"> DMARD-biologics Rheumatoid arthritis 	Thakur et al, 2016 ⁵⁰	Research article	<ul style="list-style-type: none"> Survey, N = 220 patients.
			<ul style="list-style-type: none"> Questionnaires to evaluate patient perceptions and preferences, ranking of attributes patient most preferred.
			<ul style="list-style-type: none"> Comparison of two etanercept-charged autoinjectors.
	Schiff et al, 2016 ⁵¹	Research article	<ul style="list-style-type: none"> Two simulated-use studies with no drug: formative with N = 54 patients and summative with N = 99 patients.
			<ul style="list-style-type: none"> Assessments: usability, acceptability and patient perceptions (comfort, control, ease of use, confidence of dose).
			<ul style="list-style-type: none"> Evaluation of abatacept autoinjector.
			<ul style="list-style-type: none"> Results: usability without error-patterns, high acceptability, preference over competitors in those experienced patients.
	Schulze-Koops et al, 2015 ⁵²	Research article	<ul style="list-style-type: none"> GO-MORE clinical trial [non-randomized (parallel assignment), open-label, multinational], N = 3280 patients.
			<ul style="list-style-type: none"> Efficacy outcomes.
			<ul style="list-style-type: none"> Golimumab treatment: comparison of administered injections vs self-injections by an injector.
			<ul style="list-style-type: none"> Results: patients self-injected less baseline disease activity.
	Kivitz et al, 2018 ⁵⁴	Research article	<ul style="list-style-type: none"> EASY clinical trial (randomized, open-label, multicenter, parallel-group), N = 217 active-to-severe RA patients.
			<ul style="list-style-type: none"> Assessments: device robustness and usability, patient perceptions (diaries, survey) and satisfaction, pharmacokinetics, safety and efficacy.
			<ul style="list-style-type: none"> Sarilumab: comparison of a single-use disposable pen vs prefilled syringes
			<ul style="list-style-type: none"> Patient were satisfied and confident with the pen and also found it easy to use.

Abbreviations: DM2, type 2 diabetes mellitus; MPR, medication possession ratio; QoL, quality of life; RA, rheumatoid arthritis.

the use of devices for self-injection have also been demonstrated with currently available devices for golimumab⁵² and sarilumab.⁵⁴ These are encouraging results if we consider that a good perception and tolerance of self-administration is among the patient-related factors that influence medication adherence, which, in turn, is essential for long-term efficacy.

Pen/Autoinjector Devices versus Prefilled Syringes in the Administration of MTX

To address potential problems with injections such as patient grip and dexterity limitations, various injection technologies such as autoinjection devices have been introduced, which are designed to improve the ease of use, safety and reliability of injections, and to reduce pain. Also, frequently, patients

associate SC injections with pain, discomfort, blood, and cross infection.⁵⁵ Autoinjectors automatically insert the needle and deliver a controlled dose of drug, such as the disease-modifying drugs used by patients with RA. Autoinjectors have been shown to provide a number of benefits, including a reduced risk of injection site reactions, reduced discomfort, and greater ease of use compared with manual (syringe plus needle) injections.⁴⁷

Several studies have been performed to assess self-administration devices of MTX for RA and other immune-mediated inflammatory joint and skin diseases. MTX autoinjectors, for example, enable the SC administration without the need for opening a vial, handling a needle, or preparing and operating a syringe.

In a Phase 2 clinical trial in patients with RA who had functional limitations, the MTX autoinjector was well tolerated and easy to use in the view of patients with RA and their functional limitations.⁵³ The device was rated easy to use by 98%, and instructions clear and easy to follow by 100% of patients. The authors concluded that improving SC methotrexate delivery may increase patient tolerance of self-administration, possibly improving adherence.⁵³

In a randomized crossover study comparing the pre-filled pen containing (MTX) Metex[®]/Metoject[®] PEN with the reference MTX prefilled syringe in 120 patients requiring initiation or intensification of MTX therapy for RA,⁵⁵ 76% of patients expressed their overall preference with the MTX pre-filled pen over the prefilled syringe after 6 weeks of treatment, as well as their preference in terms of use, acceptability and satisfaction with the pen. This positive perception of the prefilled-pen was further supported by the healthcare personnel involved in the study. Findings from other study designed to assess the usability, label comprehension, robustness, bioavailability, and safety of SC self-administration of MTX using the same MTX pen concluded that the pen was a viable delivery system attending to patient perceptions for patient candidates to SC MTX.⁵⁶ The first attempt to use of MTX pen was successful, comfortable, and safe with all adverse events of mild intensity observed.⁵⁶ Patients also indicated that MTX pen seemed even more convenient than oral MTX, and many of them were especially satisfied with the relative pain-free. These studies are summarized in Table 2.

Discussion

Treatment nonadherence is a major issue in contemporary medicine, particularly in chronic diseases, compromising the efficacy of a treatment. The development and implementation of medications delivered SC via autoinjector/pen devices and single-use syringes have become increasingly common for the treatment of chronic disorders such as RA. Newer injection technologies have been designed to improve the ease of use, reliability and safety as well as to minimize injection pain. Importantly, patients with RA and other chronic disorders have been found to prefer pen devices when compared to more conventional methods of treatment administration such as syringes in clinical trials.^{47,50–52,54,55}

Strategies to be implemented in clinical practice for inquiring about patients' preferences have been described,^{1–3,9,11} and its integration in the decision-making process seems to be justified. In this regard, several reviews

have confirmed that a wide range of interventions can improve medication adherence⁵⁷ and that patients with several chronic disorders entered into support programs to assist them with nurse support, medication reminders, injection training, and pen disposal reported greater adherence and persistence, and lower total costs.⁵⁸ The reduction of total healthcare costs due to improved adherence was demonstrated in patients with DM2 who used insulin pens.⁵⁹

The importance of SC MTX in the management of RA is clear given its favorable bioavailability and pharmacodynamic profile over oral delivery.^{16–20,22,27} Consequently, the potential benefits in clinical outcomes need to be explored with more real-world data and cost-effectiveness studies to support its use as part of the management of patients with RA. In fact, in patients with RA intolerant or with an inadequate response to oral MTX, the switch to SC MTX has demonstrated to improve disease control and delay the time of beginning a biological agent.⁵⁶ However, patients with RA may have difficulty in manipulating and self-administering SC MTX syringes and other SC therapies. Also, many patients associate SC administration with pain and discomfort, which, in turn, leads to less motivated patients and less likely to be adherent. Therefore, attempts to address potential problems with injections such as auto-injection devices with automatically insert the needle and deliver a controlled dose of drug have been introduced.

Pen devices seem to meet the expectations of the patients, not only in RA but in a wide number of chronic disorders and current evidence shows that they are preferred over conventional methods of treatment administration. The high level of usability and satisfaction with MTX pre-filled pens, regardless of the level of dexterity, is also supported by the perceptions of the healthcare personnel. Our search strategy demonstrated that there are no specific studies in RA that directly addressed the relationship between the use of autoinjector pens and treatment adherence, so we encourage the scientific community to further explore this issue. The current evidence assessing the usability, tolerability and convenience of distinct systems of SC MTX delivery have not directly evaluated the potential benefits in patient's adherence. However, data from other chronic diseases pointed out that optimized drug-administration systems increase patient adherence and, probably, improve disease outcomes. Further studies are warranted to explore any area of improvement in the personal, professional and social performance of the patients with RA.

Table 2 Reports Studying MTX Pen/Autoinjectors

Reference	Summary	Device	Variables	Main Outcomes
Freundlich et al, 2014 ⁵³	Phase II clinical trial (NCT01618955) to assess the performance of an MTX autoinjector together with the subject perceptions about it in RA patients with physical limitations.	OTREXUP® (methotrexate)	<ul style="list-style-type: none"> • Device: reliability and robustness. 	<ul style="list-style-type: none"> • All devices correctly functioned.
	N = 101 patients.		<ul style="list-style-type: none"> • Patient safety, local tolerance, and ease of use. 	<ul style="list-style-type: none"> • 98% agreed or strongly agreed device is easy to use. • All patients agreed that the instructions and training were easy to follow. • Patient experienced minimal site-injection pain (VAS scores were minimal). • ≈ 92% of patients noted no erythema. • There were no adverse events related to the study.
Demary et al, 2014 ⁵⁵	Phase III clinical trial (NCT01793259) to compare (through crossover design) subject perceptions about two formats of analogous devices, prefilled syringe versus prefilled pens, in RA patients.	(methotrexate) PEN	<ul style="list-style-type: none"> • Preference. 	<ul style="list-style-type: none"> • 75% of patients and 92% of nurses and investigators preferred the pen over the syringe.
	N = 120 patients.		<ul style="list-style-type: none"> • Ease of use. • Acceptability. • Satisfaction. • Local tolerability. • Safety 	<ul style="list-style-type: none"> • 73–76% of patients preferred the pen in relation to use, acceptability and satisfaction. • Differences in local tolerability between both devices were found for pain and redness. • ≈ 32% of patients suffered adverse events, being the most frequent infections and infestations.
Pachon et al, 2014 ⁵⁶	Clinical trial (NCT01871961) to assess the performance of an MTX autoinjector together with the subject perceptions about it in RA patients.	(methotrexate) PEN	<ul style="list-style-type: none"> • Patient perception of usability and label comprehension. 	<ul style="list-style-type: none"> • Between 90 and 100% of the patients found “very easy” tasks proposed in 4 scenarios.
	N = 105 patients.		<ul style="list-style-type: none"> • Device robustness. • Pharmacokinetics. 	<ul style="list-style-type: none"> • ≈ 98% of patients scored 80% in the written exam after the training. • ≈ 98% of patients scored 80% in the written exam after the training. • Within all the pens employed, one had liquid leak and another had a bent needle.

Abbreviations: MTX, methotrexate; RA, rheumatoid arthritis; VAS, visual analogue scale.

A potential limitation of this review could be that it does not explore the benefits of self-administration systems for pediatric patients despite the undeniable influence of treatment adherence in this population too. We aimed to review how the use of MTX self-injection devices can improve treatment experience, but since there is a lack of evidence on the benefits of MTX self-injection devices in children, we did not explore jointly adult and pediatric population. However, given the barriers to the administration of parenteral formulations in children and young people we consider that all the main conclusions presented here could be extrapolated from the review population to pediatric setting. Studies specifically driven to understand the factors influencing children and parent/carer attitudes to treatment adherence are required to reinforce these conclusions and align the design of administration devices for pediatric use more to patient needs.

In children and adolescents, MTX also constitutes the mainstay treatment for many of the chronic inflammatory diseases, given its demonstrated effectiveness both in oral and SC formulations. The most common use in pediatric population corresponds to juvenile idiopathic arthritis (JIA), especially polyarticular and oligoarticular and uveitis associated or not with JIA.^{60–68} Until recently, oral tablets have been the preferred form of administration in pediatric patients, reserving SC administration for those requiring weekly doses of at least 15 mg/m² or have intolerance or psychological aversion.^{63,69} In routine practice, it is usual to intensify the treatment with MTX by switching to the SC route before starting biologic agents. As in adults, adherence evaluation is not standardized in pediatrics although it is assumed as the number of missed doses of those prescribed for a specified period of time. Factors of poor adherence and persistence to MTX would be assumed similar in pediatrics and adults keeping in mind the following features:

- Patient's age: in children, adherence mainly depends on the attitude of parents or carers. However, non-compliance in adolescents is probably more frequent due to the inherent characteristics of this age of a need for independence and self-affirmation. The use of self-injectable devices in adolescents would favor adherence to methotrexate as this form of administration reduces parental guidance or health-care personnel supervision. The procedure of self-

injection would therefore help the patients maintain independence and promote their maturity.

- Abilities of patients for using injectables. Patients with RA and to lesser extent children with JIA may be limited in their ability to self-administer conventional injectables due to the involvement of hand joints. The easier and faster procedure of using self-injectable devices would favor the administration of SC methotrexate in this group of patients.
- Side effects and patient tolerance: many children develop psychological aversion to methotrexate including anticipatory nausea or behavioral distress before its administration. In such cases, switching from oral to SC administration anticipates possible improved adherence.
- Fear of needles and pain associated with the injection that is so traumatic for children could be reduced with self-injection. Also, the lower incidence of site skin reactions observed with the use of auto-injectors compared with syringes may reduce the significant impact they have on patient compliance with chronic injectable treatments, especially in pediatric population where local skin reactions may trigger discomfort and phobias. Even the lower required training to self-injecting medication compared to syringes is key to improve adherence and reduce the visits to health-care centers while saving costs.

Conclusion

Patients with RA intolerant or with an inadequate response to oral MTX have demonstrated to improve disease control as a result of switching to SC MTX. Even though patients with RA may have difficulty in manipulating and self-administering SC MTX syringes and other SC therapies, the introduction of autoinjection devices, which allows automatically insert the needle and deliver a controlled dose of drug, has demonstrated that self-injection versus injection by health care workers may increase treatment adherence and, consequently, reduce costs by decreasing the frequency of hospital visits.

Overall, data reported here highlight the value of the autoinjection in patients with RA as a means to adapt their treatment to specific needs, improve the injection experience by mitigating the fear and anxiety, overcome the challenges resulting from hand dexterity problems, and empower them to take control of their treatment journey. By optimizing SC delivery of therapies, preference and satisfaction will improve, potentially improving adherence

and treatment outcomes. This is especially important in chronic diseases where proper therapeutic adherence may be as efficient as any medical progress.

Abbreviations

ACR/ARHP, American College of Rheumatology's annual meeting; AUC, area under the curve; CQR, compliance questionnaire rheumatology; DMARDs, disease-modifying antirheumatic drugs; DM2, type 2 diabetes mellitus; EULAR, European League Against Rheumatism; JIA, juvenile idiopathic arthritis; QoL, quality of life; MARS-5, medication adherence report scale; MEMS, medication event monitoring system; MESH, medical subject headings; MPR, medication possession ratio; MTX, methotrexate; RA, rheumatoid arthritis; SC, Subcutaneous; VAS, visual analogue scale; WHO, World Health Organization.

Author Contributions

All authors have substantially (i) contributed to the acquisition, analysis or interpretation of data, (ii) drafted the manuscript and critically revised the manuscript for important intellectual content, (iii) have agreed on the journal which the article will be submitted, (iv) gave final approval of the version to be published, and (v) agreed to take responsibility and be accountable for the contents of the article.

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