Does different administration method of methotrexate matter in early rheumatoid arthritis? An exploratory register-based study

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Abstract

Objective

We aimed to study the course of disease activity and pain over two years in patients with early rheumatoid arthritis who began subcutaneous (SC) or peroral (PO) methotrexate (MTX) as part of their first treatment strategy. Treatment failures and drug survival were analysed.

Methods

Patients who received a new reimbursement for RA between 1.1.2016 to 31.12.2023 were identified in the Reimbursement Register; purchases of DMARDs were available in the Drug Purchase Register. Clinical and demographic data were extracted from the Finnish Rheumatology Quality Register. Locally estimated scatterplot smoothing (LOESS) trajectories were used to illustrate the development of disease activity and pain for two years. Treatment failures, defined as the probability to avoid bDMARDs, were analysed with Cox regression, adjusted for age and sex. The proportion of patients taking MTX at two years were calculated.

Results

From the database, we identified 4,655 patients (mean age 60 years, 64% female, 80% seropositive) who started MTX as part of the initial medication for early RA. MTX SC was purchased by 1076(23.1%) and MTX PO by 3579(76.9%) patients. At baseline, the mean (SD) DAS28 was 3.8(1.2) for MTX SC starters and 3.9(1.2) for MTX PO starters. The trajectories for disease activity and pain were more favourable for two years in patients with initial MTX SC versus PO. The probability (95%CI) to avoid bDMARDs was 0.87(0.85 to 0.89) for MTX SC and 0.91(0.90 to 0.92) for MTX PO starters (p<0.001). At two years, MTX was purchased by 80% and 79% of patients who started with MTX SC versus PO, respectively.

Conclusion

Our study provides real-world evidence of the use MTX SC and PO as part of the first treatment strategy for RA. Starting with MTX, SC may be more favourable for patients, in terms of disease activity and pain, over the following two years.

Key words

methotrexate, subcutaneous, administration method, rheumatoid arthritis

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Introduction

In early RA, remission should be achieved as fast as possible. Therefore, the initial treatment strategy should be remission-inducing in its full meaning. Randomised clinical trials provide evidence of the superiority of biologic disease-modifying anti-rheumatic drugs (bDMARDs) over conventional synthetic (cs)DMARDs: The NORDSTAR trial showed high and similar adjusted CDAI remission rates at 48 weeks in the three bDMARD arms with methotrexate (MTX), compared to lower rates in the active conventional therapy arm with MTX (with csDMARDs or oral glucocorticoids) (1). In the NEO-RACo trial back in 2013, the DAS28 remission was met at 3 months by 88% *versus* 64% of patients who received infliximab-intensified triple combination *versus* triple combination only (2). In the SWEFOT trial, with peroral (PO) MTX as the initial therapy, only 30% of patients had low disease activity at the check-up visit after 3–4 months (3). However, according to the EULAR recommendations (4), the initial treatment strategy for early RA is still MTX with or without other csDMARDs. Reimbursement policies and many other obstacles may prevent the use of others than csDMARDs as the initial therapy in early RA in many countries (5). Therefore, optimising the administration of MTX in early RA is highly important.

MTX has been established as the anchor drug in the treatment of RA, with prescription rates of up to 91% for RA patients during the disease course (6-9). MTX is administered either PO or subcutaneously (SC) and there is so far no consensus for its preferred route of administration (7). Previous research suggests that there are differences between SC and PO routes in terms of bioavailability, efficacy and tolerability in the treatment of RA, though the results are somewhat contradictory (10, 11). For example, systematic literature reviews suggest that a higher AUC_{t-0} can be achieved with SC administration of MTX, with one study of 65 healthy subjects showing differences of 203–1146 h·ng/mL depending on the dose (7.5–22.5 mg). With MTX PO, the AUC_{t-0} has been shown to plateau at a little over 1800 ng/ml with doses of ≥15 mg, whereas with MTX SC, it increases linearly depending on the dose, up to approximately 2700 ng/ml with doses of 25 mg. In addition, MTX SC has a shorter time to achieve maximum observed concentration, as well as a shorter half-time (12-14). The factors for differences in pharmacokinetics include receptor saturation, inhibitory effect of food in the gastrointestinal (GI) tract and increased metabolisation by gut flora (15).

SC administration of MTX has been shown to cause less GI-related adverse effects, such as nausea and diarrhoea in most studies (12). However, a follow-up study of 3–6 months showed slightly more GI symptoms in SC users compared to PO users (29% *vs*. 27%) (16). Possibly partly due to the differences in GI adverse effects, several studies report superior tolerability for MTX SC than PO. According to a follow-up study of 666 patients with early RA, 49% of patients with MTX SC as the initial therapy changed treatment, compared to 77% on MTX PO. Inefficacy was the cause for a switch in 59% of PO and 28% of SC users (17, 18). Additionally, higher patient satisfaction, as well as less discomfort and a higher quality of life were associated with the use of MTX SC (8).

To acquire real-world evidence of the use of MTX SC *versus* PO as part of the first treatment strategy in early RA, we utilised the Finnish Rheumatology Quality Register and national administrative registers. These registries were used to study the course of disease activity and patient reported pain over two years as well as treatment failures and drug survival.

Methods

Source of data

Patients with incident RA are diagnosed in rheumatology outpatient clinics, where they receive initial DMARD prescriptions according to the national guidelines together with a medication reimbursement application, which is prepared by a rheumatologist. Reimbursement for DMARDs is granted by the Social Insurance Institution of Finland (KELA). The Reimbursement Register

Table I. Baseline data of patients with early rheumatoid arthritis who began methotrexate (MTX) as part of the first treatment strategy, according to the route of administration.

Variable	Available data, all patients, %	All patients	Available data, MTX PO, %	MTX PO	Available data MTX SC, %	MTX SC	*p*-value
Number of patients		4655		3579		1076	
Mean (SD) age in years	100%	59.8 (14.7)	100%	60.3 (14.7)	100%	58.4 (14.7)	<0.001
Proportion of female patients, %	100%	63.9%	100%	63.4%	100%	65.6%	0.203
Proportion of seropositive patients, %	84%	79.5%	81%	75.8%	93%	90.2%	<0.001
Proportion of ACPA-positive patients, %	83%	72.7%	80%	68.3%	93%	85.5%	<0.001
DAS28, mean (SD)	60%	3.9 (1.2)	56%	3.9 (1.2)	75%	3.8 (1.2)	0.009
Pain, mean (SD)	61%	51 (27)	57%	51 (27)	74%	51 (26)	0.95
Comorbidities							
Depression	100%	12.6%	100%	12.4%	100%	13.1%	0.597
Anxiety	100%	6.0%	100%	5.8%	100%	6.6%	0.398
Fibromyalgia	100%	2.1%	100%	2.0%	100%	2.4%	0.528
Sleep apnea	100%	11.1%	100%	11.2%	100%	10.8%	0.740
Concomitant medication							
Triple combination therapy	100%	34.1%	100%	34.8%	100%	31.8%	0.072
Glucocorticoids	100%	61.7%	100%	64.9%	100%	51.2%	<0.001

MTX: methotrexate; PO: peroral; SC: subcutaneous; SD: standard deviation; ACPA: anti-citrullinated protein antibody; DAS28: Disease Activity Score 28; Triple combination therapy: MTX, sulfasalazine and hydroxychloroquine.

contains an ICD code for the diagnosis and the date of the approval. KELA also maintains The Drug Purchase Register for all medications that need a prescription, which contains dates and amounts of medication purchases.

Monitoring tools such as GoTreatIT Rheuma, BCB and RaiQu are used in almost all rheumatology outpatient clinics in Finland to facilitate treatment decisions in common clinical practice and to accumulate patient data for secondary purposes such as medial research. The data includes clinical data such as demographics, measures for disease activity, and patient reported outcomes such as pain. Data from different health care districts are collected in the Finnish Rheumatology Quality Register which is maintained by the Institute for Health and Welfare (THL). Data regarding comorbidities were collected from the Hospital Discharge Register (HILMO) and Finnish Care Register (avoHILMO), which contain diagnoses determined by treating physicians. Both are upheld by the THL. The HILMO database covers all dates and causes of hospitalisation and outpatient care since 1969. AvoHILMO includes all primary health care contacts and visits at health centres, and it was first introduced in 2011. The diagnoses have been coded according to the Finnish version of ICD-10.

The Finnish Rheumatology Quality Register, HILMO, avoHILMO and KELA-databases were utilised in this study. Patient data between registries were linked using a unique personal identification code.

Database

All patients who received a new reimbursement for RA between 1.1.2016 to 31.12.2023 were identified in the Reimbursement Register, with the reimbursement approval date as the index date. Clinical data were extracted from the Finnish Rheumatology Quality Register. Patients who purchased methotrexate (MTX) ± 90 days within the index date with or without other csDMARDs such as hydroxychloroquine (HCQ) and sulfasalazine (SSZ) and with no prior DMARD use, excluding glucocorticoids (CS), were included in this study. All patients were at least 18 years old and were not diagnosed with any other specific arthritides than RA.

Variables

Demographic data included sex and age. Patients were seropositive if they had a positive titre for rheumatoid factor (RF) and/or antibodies for anti-citrullinated proteins (ACPA). A level of ≥15 IU/mL was considered elevated for RF and a level of ≥7 kU/L for ACPA according to the Finnish laboratory reference values. The disease activity score DAS28 was used to describe the clinical activity of RA. Patient self-reported pain was measured on the 0–100 mm Visual Analogue scale (VAS), where 0 stands for no symptoms and 100 mm for maximum intensity. The prevalence of several comorbidities that affect patients' self-reported pain were analysed. In this study, we included fibromyalgia (M79.7), sleep apnea (G47.3), any diagnosis for a depressive disorder (F32.0–32.9, F33.0–33.3, F33.8, F33.9, F34.1, and F41.2) and any diagnosis for an anxiety related disorder (F40–F42). The use of concomitant medication used alongside MTX was analysed. In this study, we included combination therapy with HCQ and SSZ, or GCs as variables.

Statistical methods

Two groups were compared. MTX SC refers to RA patients who started MTX SC as their initial DMARD as a monotherapy or in combination with other csDMARDs. MTX PO refers to RA patients who started MTX PO as their initial DMARD as a monotherapy or in

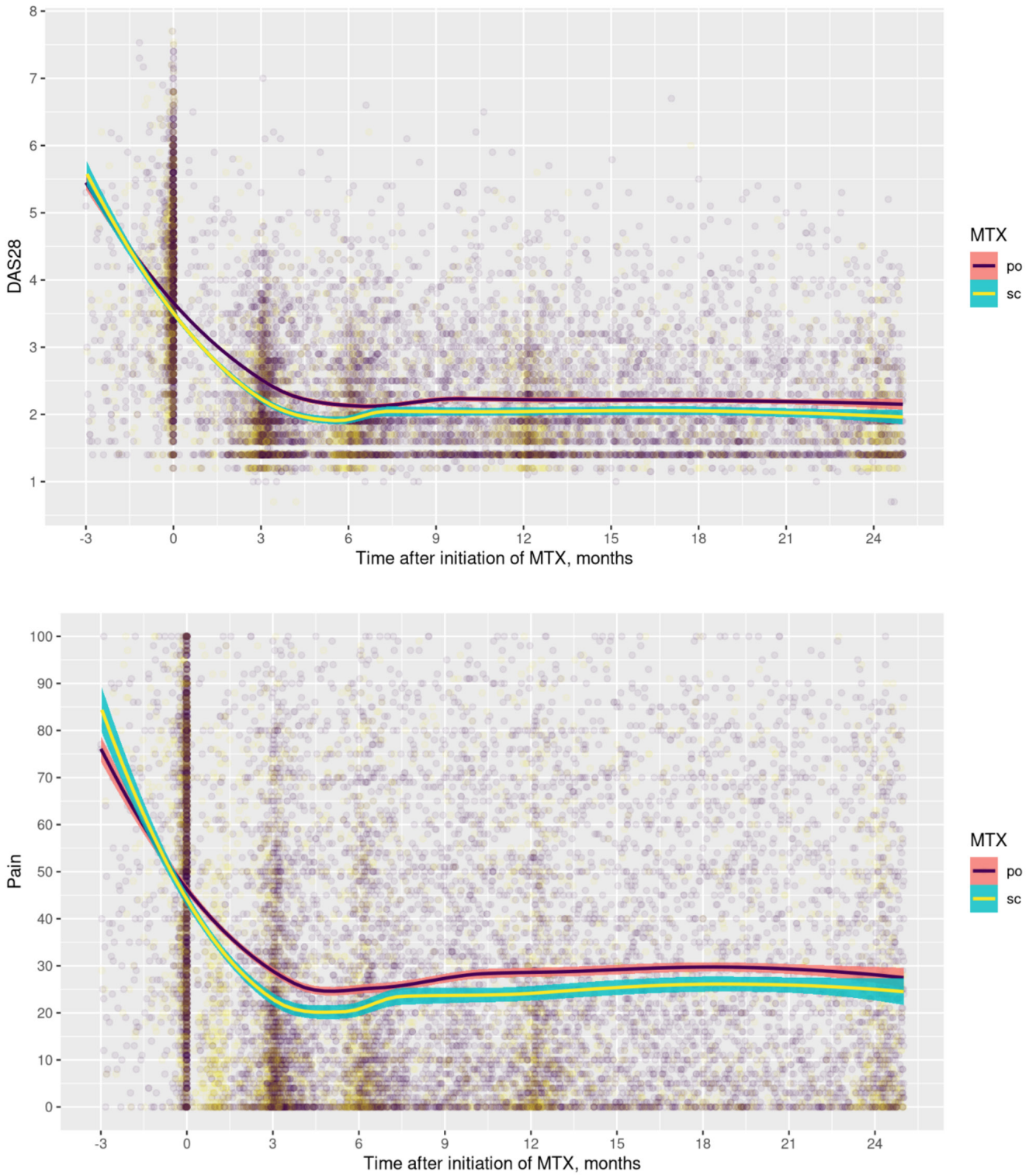

Fig. 1. Development of disease activity and pain in patients with early rheumatoid arthritis, according to the initial treatment of peroral (po) or subcutaneous (sc) methotrexate (MTX). Plots of the locally estimated scatterplot smoothing (LOESS) trajectories over individual values, with 95% CI.

combination with other csDMARDs. The period of interest was the first two years after the start of treatment (*i.e.* purchase of the first MTX) for early RA.

All values of disease activity were plotted for all patients who started MTX SC or MTX PO, including up to 90 days before the first purchase of MTX (time = 0), and for the following 24 months. Locally estimated scatterplot smoothing (LOESS) trajectories (with 95% confidence interval, CI) were used to illustrate the development of disease activity over individual patient data, over the following two years. The same statistics were used to plot patient-reported pain.

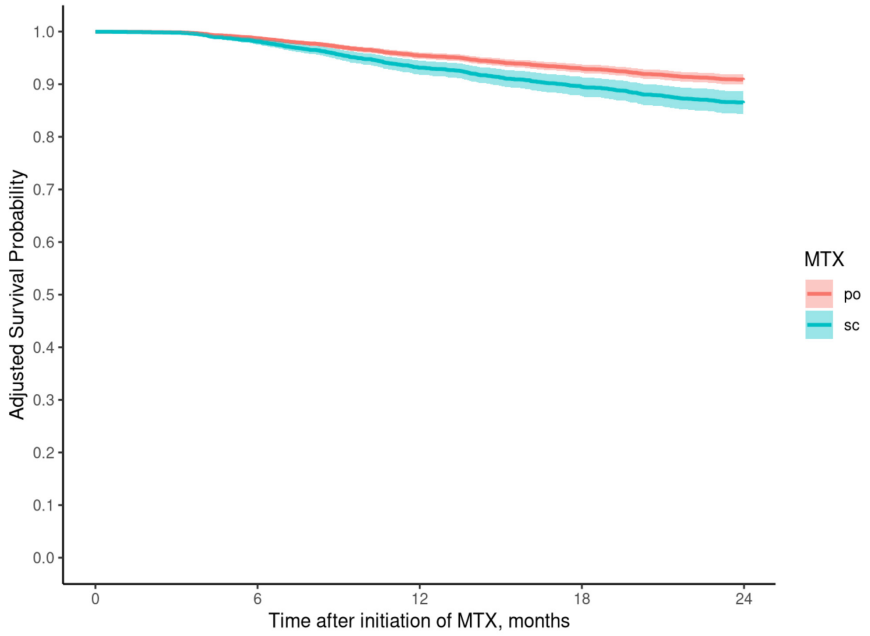

Fig. 2. The probability to avoid bDMARD initiation over 24 months, in patients who started subcutaneous (sc) or peroral (po) methotrexate (MTX).

Treatment failure, defined as a start of a bDMARD, was compared between the groups MTX SC *versus* MTX PO, using Cox regression analysis and visualised by survival curves over two years, with a log-rank *p*-value, adjusted for age and sex.

As a proxy for drug survival of MTX therapy, we calculated a proportion of patients who purchased any MTX at 24 (±6) months after the initiation. In this calculation, we included patients who reached the follow up point of two years: 807 of 1076 who started MTX SC and 3263 or 3579 who started MTX PO.

A *p*-value of 0.05 was set as a threshold for statistical significance. Categorical variables were described using frequency counts and percentages. Continuous variables were described using means and 95% confidence intervals. Analyses were conducted using the R Statistical language on Ubuntu 20.04.5 LTS.

Ethics

This study was conducted as a register-based study and approval for the study, as well as permission to use patient data for secondary purposes was granted by the THL. The data used in this study was pseudonymised and patient consent was not required in this study setting.

Results

Baseline data

A total of 6,416 patients with incipient RA were identified. MTX was purchased by 5731 (89.3%) of all patients. Among 4655 patients, MTX was purchased within 90 days of the index date: MTX SC by 1076 (23.1%) and MTX PO by 3579 (76.9%) of the patients. For the rest, MTX had been purchased more than 90 days before or after the index visit and they were excluded from the analysis.

The average age of all patients was 59.8 years, 63.9% were female, and 79.5% were seropositive. Those who started MTX SC, were significantly more often seropositive than those who started MTX PO. The values of clinical measures were similar between the groups at baseline (Table I). The prevalence of depression, anxiety, fibromyalgia and sleep apnea were similar between MTX SC and MTX PO users. MTX PO users had slightly more often combination therapy (p=0.072) and significantly more often GCs (p<0.001) as concomitant medication alongside MTX at baseline (Table I).

Trajectories for disease activity and pain

The trajectories for disease activity and pain were calculated from up to 90 days before the first purchase of MTX (time = 0) and for 24 months thereafter. The graphs indicate that both disease activity and pain had a more favourable course for patients who started MTX SC *versus* MTX PO, especially within the first months after starting the medications (Fig. 1).

Treatment failures

The treatment failure was defined as a start of a bDMARD. The probability (95%CI) to avoid bDMARDs was 0.87 (0.85 to 0.89) for those who started MTX SC and 0.91 (0.90 to 0.92) for MTX PO starters, adjusted for age and sex (p<0.001) (Fig. 2).

Drug survival

At 24 (± 6) months, a similar proportion of patients had purchased any MTX: 80% of patients who started with MTX SC and 79% of patients who started with MTX PO.

Discussion

Real-world data from the Finnish Rheumatology Quality Register suggest that the initial route of MTX administration influences the levels of disease activity and patient reported pain, over the following two years, in patients with early RA. Our study suggests that MTX SC may provide greater clinical benefits to the patients, compared to MTX PO, as part of the initial treatment strategy even when the use of GCs was more prevalent among patients who used MTX PO *versus* MTX SC (64.9% *vs*. 51.2%).

A number of meta-analyses and systematic literature reviews have recently addressed the question of the administration method of MTX, based on RCTs and other types of studies. Overall, there appears at least a tendency of MTX SC being better than MTX PO, in general rheumatology endpoints such as ACR20 response or reduction of DAS28, measured 3 to 6 months after MTX initiation (11, 19). Up to 85% remission rates at 3 months have been seen in patients with RA treated with MTX SC (7). According to a meta-analysis in 2019, MTX SC had an OR of 3.02 for achieving ACR20 compared to a PO route (20).

Even though MTX PO has a bioavailability of 93% with a dose of 7.5 mg/week (21), its bioavailability ranges between 30 to 70% with doses of 10 mg/week to 15 mg/week (22). As was previously mentioned, higher concentrations of MTX in the circulatory system with similar dosage can be achieved with SC route of administration as well as a higher maximum concentration of 2700 ng/ml, compared to PO route of administration (13, 14). Inside the cells, MTX is polyglutamated (PG) to MTXPG, which produces the anti-inflammatory effect by inhibiting folylpolyglutamate synthase enzyme and other folate pathway enzymes. Factors that affect the concentrations of MTXPG include age, renal function and MTX dose. In addition to producing a higher concentration in the circulatory system, the use of SC MTX has been linked with increased levels of long-chain MTXPGs, which provide a much more potent inhibition of target enzymes within folate metabolism (22, 23). Possibly due to these factors, SC MTX seems to produce a faster clinical response compared to PO MTX. In a previous follow-up study conducted with 137 patients receiving PO MTX and GCs and 80 patients receiving SC MTX, SSZ and HCQ and intra-articular GCs, 55% of patients with SC MTX and combinatory therapy had a CDAI of ≤2.8, and the same number was 36% for PO MTX users with GCs at week 48. Similar differences were seen for patient global VAS and tender joint counts (24). In our study, a higher reduction was seen for pain and DAS28 at 3 months for SC MTX users compared to PO MTX users, though the difference evened out slightly at 6 months.

In our study, about 80% of patients were taking MTX at two years, regardless of the initial route of administration. Twelve-month continuation rates of MTX PO of 73–75% have been reported. In addition, switching to MTX SC after treatment failure with PO MTX has been shown to result in high continuation rates of treatment, 47% of patients were still using MTX at 5 years and only <10% of patients required bDMARDs during 2 years after the switch (25). In our study, slightly more patients with initial MTX SC started a bDMARD over the following two years, compared to MTX PO as the initial therapy. However, the likelihood to start a biologic over two years was less than 15% in both groups and is at a similar level as in the Italian early RA MITRA cohort where 12.7% of patients started a bDMARD over 18 months (26).

Limitations

Limitations of our study include general limitations of register-based studies, including missing data. At the baseline, data for seropositivity were available in 93% of patients in the MTX SC group and in 81% of patients in the MTX PO group. For clinical measures, the baseline data were missing in almost 45% of patients in the MTX PO group *versus* 25% in the MTX SC group. Another major limitation is that although a trajectory analysis is a robust method to illustrate data, it does not allow for definitive conclusions regarding the superiority of one MTX administration route over the other. Furthermore, the trajectories only illustrate the following two years after the baseline (here: the initial administration method of MTX) without providing reasons for the phenomenon (here: cases whose initial medication was already switched from SC to PO route or *vice versa*, or to another medication such as a bDMARD, were included). Therefore, the initial administration method of MTX SC may merely indicate an overall more active approach to treat patients with early RA.

Conclusions

Despite limitations, our study provides valuable real-world data concerning the initial administration method of MTX in a considerable number of patients with early RA.

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