

# Effectiveness of subcutaneously administered methotrexate in patients with rheumatoid arthritis

Przemysław Kotyla<sup>1,C,D,F</sup>, Bogdan Batko<sup>2,E,F</sup>, Zbigniew Zuber<sup>3,E,F</sup>,  
Agnieszka Almgren-Rachtan<sup>4,B,C,F</sup>, Jerzy Chudek<sup>5,A,C-F</sup>, Eugeniusz Józef Kucharz<sup>1,C,F</sup>

<sup>1</sup> Department of Internal Medicine, Rheumatology and Clinical Immunology, Medical Faculty in Katowice, Medical University of Silesia, Katowice, Poland

<sup>2</sup> Department of Rheumatology, J. Dietl Specialist Hospital, Kraków, Poland

<sup>3</sup> Department of Older Children with Subunits of Neurology and Rheumatology, St. Louis Regional Specialized Children's Hospital, Kraków, Poland

<sup>4</sup> Department of Pharmacovigilance, Europharma M. Rachtan Co. Ltd., Katowice, Poland

<sup>5</sup> Department of Pathophysiology and Department of Internal Medicine and Oncological Chemotherapy, Medical University of Silesia, Katowice, Poland

A – research concept and design; B – collection and/or assembly of data; C – data analysis and interpretation;

D – writing the article; E – critical revision of the article; F – final approval of the article

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## Address for correspondence

Przemysław Kotyla  
E-mail: [pjkotyła@gmail.com](mailto:pjkotyła@gmail.com)

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## Conflict of interest

None declared

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## Abstract

**Background.** Subcutaneous methotrexate (sMTX) administration is considered more effective than the oral route due to better bioavailability and a lower rate of adverse drug reactions (ADRs); however, clinical data supporting this hypothesis is scarce.

**Objectives.** The aim of the study was to evaluate the efficacy and tolerability of sMTX in patients with active rheumatoid arthritis (RA), including a subset classified as an early stage of RA.

**Material and methods.** A post-marketing, multicenter, open-label, non-randomized, non-interventional study enrolled 771 adult patients with active RA treated with sMTX (Metex<sup>®</sup>) for 2–6 weeks. The evaluation of therapy effectiveness (DAS28-ESR or DAS28-CRP) and monitoring of ADRs was an element of routine patient management. Therapy effectiveness was scored as the achievement of remission or response (according to European League Against Rheumatism (EULAR)).

**Results.** Among 761 (98.7%) patients that continued sMTX (after 25–31 weeks), clinical response was achieved by 69.5%, remission by 19.2% and low disease activity by 34.2%. Patients aged >60 years were less likely to achieve both remission (odds ratio (OR) = 0.61 (95% confidence interval (95% CI) = 0.39–0.93)) and clinical response (OR = 0.82 (95% CI = 0.71–0.95)), while overweight/obese patients (OR = 1.11 (95% CI = 1.00–1.24)) and those with early RA had greater chance to reach a clinical response (OR = 1.18 (95% CI = 1.03–1.34)). There were 16 ADRs (no serious or severe). In addition, at least 2-fold increase in alanine transaminase (ALT) activity was noted in 10 patients (1.3%).

**Conclusions.** After 6-month therapy with sMTX, about 70% of patients with RA achieve a clinical response, and remission was observed in 20%. Younger age, overweight/obesity and an early stage of the disease are factors increasing therapy effectiveness; sMTX is well tolerated.

**Key words:** methotrexate, rheumatoid arthritis, tolerance, subcutaneous, response rate

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## Introduction

Rheumatoid arthritis (RA) is the most common form of inflammatory arthropathy and affects 1–2% of the population worldwide.<sup>1</sup> The disease may have a clinical course that is difficult to predict, and the vast majority of patients eventually develop the disease progression with bone erosions and structural damage to the joints followed by functional impairment and increased mortality. The management of RA is aimed to control disease activity and prevent irreversible joint damage. To achieve these goals, early and aggressive therapy is required. New therapies including anti-cytokine drugs, interleukin antagonists or B-cell-depleting agents have revolutionized the treatment of RA. However, therapy using conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) is still recognized as the first-line treatment that provides a satisfactory clinical response, especially when initiated early. The treatment of RA should be initiated with csDMARDs, a group of various chemical compounds with a not-fully-known mechanism of action, that possess the ability to target inflammation and reduce structural joint damage.

Among several csDMARDs, methotrexate (MTX; a folic acid antagonist) is still recognized as an anchor drug,<sup>2</sup> recommended by the European League Against Rheumatism (EULAR) and American College of Rheumatology (ACR) as the first-choice drug for the management of RA.<sup>3,4</sup> The recommendations point out that very early use of MTX results in higher clinical response ratio.<sup>3,4</sup> Moreover, the treatment outcome is related to the activity of the disease that patients experience throughout the period of therapy. That is why the substantial reduction of disease activity and maintenance of clinical remission are now targets of all strategies used in patients with RA. The philosophy of optimal therapy is to achieve remission or at least minimal disease activity, commonly known as “treat to target” (T2T) strategy, nowadays considered as a standard of care in daily clinical practice.<sup>5</sup>

Effective treatment should be initiated at the very early stages of the disease, otherwise known as the “window of opportunity”, when therapeutic intervention may lead to halting disease progression or even long-lasting remission.<sup>6</sup>

Recognizing MTX as the first-line treatment for all patients with RA is based on the results of numerous clinical trials. However, it is still unknown whether the route of MTX administration (orally or parenterally) may affect the outcome, which is of most significance in early stages of RA when the window of opportunity is wide open. Taking into account the better bioavailability of MTX when given parenterally, and less adverse drug reactions (ADRs), the parenteral route seems to be a better therapeutic option. Unfortunately, such therapy is more expensive and may result in patient discomfort related to injections. That is why it is important to assess whether patients treated with subcutaneous MTX (sMTX) may experience some additional benefits overshadowing the higher cost of therapy and self-injection difficulties.

The aim of the study was to evaluate the efficacy and tolerability of sMTX (Metex<sup>®</sup>; Medac Gesellschaft für klinische Spezialpräparate GmbH, Wedel, Germany) in patients with active RA, including a subset of those with an early stage of the disease.

## Material and methods

A post-marketing, multicenter, open-label, non-randomized, non-interventional study was conducted by 98 rheumatologists with the participation of 771 adult patients diagnosed with active RA on the basis of EULAR criteria.<sup>7</sup>

The only inclusion criterion was therapy with sMTX (Metex<sup>®</sup>) for 2–6 weeks before enrollment. In line with the Summary Product Characteristics, patients with hypersensitivity to MTX or any of the excipients contained in the Metex<sup>®</sup> formulation, liver failure, alcohol abuse, severe renal impairment (creatinine clearance below 20 mL/min), recognized blood dyscrasias (bone marrow hypoplasia, leukopenia, thrombocytopenia, or clinically significant anemia), interstitial lung disease, severe acute or chronic infections (tuberculosis, HIV or other immunodeficiency), ulceration of the oral mucosa, and the diagnosis of active gastric ulcer or duodenal ulcer, simultaneous vaccination with live vaccines, as well as pregnant and breastfeeding women, were excluded from the study.

The study was designed as a post-authorization efficacy study (PAES) (Register: EUPAS18973), in line with Article 1(15) of Directive 2014/357/EC, as a study related to an authorized medicinal product and conducted within an authorized therapeutic indication aim of complementing available efficacy data in the light of well-reasoned scientific uncertainties on aspects of the evidence of benefits that is to be, or can only be, addressed post-authorization. According to Polish law, PAES studies are not medical experiments and do not require either Bioethical Committee approval or the need to obtain informed consent from the patients for inclusion. As such, neither ethical approval nor informed consent from patients for inclusion into this study was sought.

The evaluation of therapy effectiveness and monitoring of ADRs was an element of routine patient management by the rheumatologists. The study methodology included a collection of effectiveness and safety data during 3 consecutive visits performed in about 12-week intervals, that is, the routine clinical check-ups during therapy. The data was entered into a study questionnaire completed within the 3 subsequent control visits between May 2015 and November 2016.

## Monitoring of subcutaneous methotrexate therapy and its effectiveness

Collection of data included: laboratory results (total blood count, erythrocyte sedimentation rate (ESR),

C-reactive protein (CRP), aspartate transaminase (AST), alanine transaminase (ALT), and creatinine – if performed); an assessment of therapy effectiveness with Methotrexate® including Disease Activity Score with 28-joint counts (DAS28), based on ESR (DAS28-ESR) or CRP (DAS28-CRP), on center discretion, performed during all 3 visits; compliance with a Medication Adherence Questionnaire (MAQ); and reported ADRs.

## Data analysis

Using body mass and height, body mass index (BMI) was calculated. Normal weight, overweight and obesity were defined according to the World Health Organization (WHO) criteria (BMI values of 18.5–24.9 kg/m<sup>2</sup>, 25–29.9 kg/m<sup>2</sup> and ≥30 kg/m<sup>2</sup>, respectively). Rheumatoid arthritis activity was scored based on DAS28-ESR or DAS28-CRP criteria (on center discretion). DAS28 of less than 2.6 indicates remission, 2.6 and higher but less than 3.2 indicates low disease activity, 3.2 and higher but less than 5.1 indicates moderate disease activity, and higher than 5.1 indicates high disease activity.<sup>8</sup> The primary endpoint was the number of patients achieving remission. The secondary endpoint was response rates defined as a decrease in DAS28 > 1.2 with the shift to a lower class activity. Adherence to sMTX was scored on the basis of the MAQ as follows: adherent (≤2 points) or non-adherent (>2 points).

## Statistical analysis

Analyses were performed using STATISTICA v. 10.0 PL (StatSoft Inc., Tulsa, USA). All data is expressed as percentages or means with standard deviation (SD). The  $\chi^2$  and  $\chi^2$  for trend tests were used to compare qualitative data. Changes in quantitative data across the visits were analyzed with a single-factor repeated-measures analysis of variance (ANOVA) for normally distributed or Friedman test for not normally distributed variables. Logistic regression analysis was used for calculation of odds ratios (OR) and 95% confidence intervals (CI). A p-value of less than 0.05 was considered statistically significant.

## Results

### Study group characteristics

The characteristics of the study group of 771 patients (mean age 56.7 ±11.3 years) diagnosed with RA is shown in Table 1. There was a high predominance of women (3.7:1). Patients with early RA (up to 6 months after the onset of symptoms) accounted for 9.5% of all studied patients.

Laboratory tests carried out before the 1<sup>st</sup> visit (treated with sMTX from 2 to 6 weeks in 70.4%) showed a more than 2-fold elevated activity of ALT and AST (>80 U/L) in 0.6%

Table 1. Study group characteristics (n = 771)

Variables	Value
Sex [n; %]	
men	163; 21.1
women	608; 78.9
Age [years]	56.7 ±11.3
BMI [kg/m <sup>2</sup> ]	
<18.5 kg/m <sup>2</sup> [n; %]	3; 0.4
18.5–24.9 kg/m <sup>2</sup> [n; %]	260; 33.7
25.0–29.9 kg/m <sup>2</sup> [n; %]	356; 46.2
≥30.0 kg/m <sup>2</sup> [n; %]	152; 19.7
Red blood cells [10 <sup>6</sup> /μL]	4.0 ±0.8
Hematocrit [%]	39.5 ±6.3
Hemoglobin [g/dL]	13.0 ±1.3
<11.0 g/dL [n; %]	37; 4.8
White blood count [10 <sup>3</sup> /μL]	7.4 ±2.3
<4 × 10 <sup>3</sup> /μL [n; %]	11; 1.4
Platelets [10 <sup>3</sup> /μL]	282 ±80
<150 × 10 <sup>3</sup> /μL [n; %]	8; 1.0
ALT [U/L]	26.0 ±20.8
>80 U/L [n; %]	5; 0.6
AST [U/L]	24.0 ±15.9
>80 U/L [n; %]	2; 0.3
Bilirubin [mg/dL]	0.73 ±0.06
Creatinine [mg/dL]	0.84 ±0.01
eGFR-MDRD [mL/min/1.73 m <sup>2</sup> ]	83.9 ±21.7
eGFR <60 mL/min/1.73 m <sup>2</sup> [n; %]	64; 8.3
Duration of RA [n; %]	
>6 months	692; 89.7
<6 months	73; 9.5
missing data	6; 0.8

BMI – body mass index; ALT – alanine transaminase; AST – aspartate transaminase; eGFR-MDRD – estimated glomerular filtration rate – modification of diet in renal disease; RA – rheumatoid arthritis.

and 0.3% of patients, respectively. Leukopenia and thrombocytopenia occurred in 1.4% and 1.0% of patients, respectively. Anemia occurred in 4.8% and chronic kidney disease (estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m<sup>2</sup>) was observed in 8.3% of patients.

At the 1<sup>st</sup> visit, 3.5% of patients already obtained remission, 10.4% presented low activity, 39.3% moderate, and 46.9% very active disease. There was no association between the disease activity and nutritional status (data not shown).

### Course of treatment with subcutaneous methotrexate

The mean weakly prescribed dose of sMTX at the 1<sup>st</sup> visit (18.0 ±4.9 mg) was increased during the subsequent 2 visits by 2.2 mg to 20.2 ±4.2 mg. There were only 2 dropouts, 1 patient did not accept the subcutaneous route of drug administration, and 6 patients discontinued therapy due to ADR occurrence. In 1 patient, therapy was discontinued due to detection of anti-HCV antibodies. According to the MAQ, the compliance to therapy was over 99% (Table 2).

**Table 2.** Effectiveness and compliance with subcutaneous methotrexate (MTX). Data shown as means  $\pm$  standard deviation (SD) or medians with interquartile range ( $\wedge$ )

Variable	Visit I [n = 771]	Visit II [n = 770]	Visit III [n = 761]	ANOVA $\chi^2$
Number of patients discontinuing therapy, n	–	1	8	–
Number of patients loss to follow-up, n	–	0	2	–
Duration of follow-up [days]	–	77 $\pm$ 20	160 $\pm$ 30	–
MTX dose [mg/week]	18.4 $\pm$ 4.5	19.6 $\pm$ 4.2	20.2 $\pm$ 4.3	<0.001
Disease activity measures:				
tender joints count, n	9.0 $\pm$ 5.4	5.9 $\pm$ 3.9	4.1 $\pm$ 3.2	<0.001
swollen joints count, n	5.7 $\pm$ 4.2	3.8 $\pm$ 3.1	2.0 $\pm$ 2.3	<0.001
patient global assessment of disease activity	56 $\pm$ 19	39 $\pm$ 17	28 $\pm$ 16	<0.001
ESR [mm/h] <sup><math>\wedge</math></sup>	30 (20–42)	20 (14–30)	16 (11–21)	<0.001
CRP [mg/L] <sup><math>\wedge</math></sup>	11.0 (6.1–18.5)	6.1 (4.0–10.8)	5.0 (3.0–7.0)	<0.001
DAS28 $\leq$ 2.6 (remission, n (%))	27 (3.5)	55 (7.3)	148 (19.2)	<0.001*
DAS28 2.6–3.2 (low activity, n (%))	80 (10.4)	144 (18.6)	264 (34.20)	<0.001*
DAS28 3.2–5.1 (moderate activity, n (%))	303 (39.3)	460 (59.7)	311 (40.3)	<0.001
DAS28 >5.1 (high activity, n (%))	361 (46.9)	111 (14.4)	48 (6.3)	<0.001*
Compliance (MAQ $\leq$ 2 points, n (%))	766 (99.3)	766 (99.3)	769 (99.7)	0.97

\* $\chi^2$  – trend; ANOVA – analysis of variance; ESR – erythrocyte sedimentation rate; CRP – C-reactive protein; DAS28 – Disease Activity Score 28; MAQ – Medical Adherence Questionnaire.

## Therapy effectiveness

Among the 761 patients continuing therapy with sMTX for 23  $\pm$ 4 weeks (3<sup>rd</sup> visit), remission was obtained by 19.2% and 34.2% achieved a low activity of the disease (Table 2). Response (decrease in DAS28 > 1.2 with a shift to a lower-class activity) was achieved by 529 patients (69.5% of included). There were 22 patients with RA exacerbation (2.9% of included) during the therapy.

Older patients (aged >60 years) were less likely to achieve both remission or response to the therapy with sMTX (OR = 0.61 (95% CI = 0.39–0.93) and 0.82 (95% CI = 0.71–0.95), respectively), while overweight/obese patients and those with early RA had a greater chance to get a response (OR = 1.11 (95% CI = 1.00–1.24) and 1.18 (1.03–1.34), respectively) (Table 3).

**Table 3.** Factors affecting the effectiveness of therapy with subcutaneous methotrexate (sMTX) in patients with RA

Factor	Variables	Patients that obtained remission during the therapy [%]	Patients that obtained response to the treatment [%]	The probability of obtaining remission during the therapy		The probability of obtaining response to the treatment	
				OR (95% CI)	p-value	OR (95% CI)	p-value
Sex	women	19.0	69.6	Ref		Ref	
	men	19.9	69.3	1.05 (0.73–1.49)	0.80	0.99 (0.88–1.12)	0.93
Age	$\leq$ 40 years	27.3	76.2	Ref		Ref	
	41–60 years	19.8	72.3	0.73 (0.49–1.09)	0.12	0.95 (0.83–1.09)	0.45
	>60 years	16.5	62.6	0.61 (0.39–0.93)	<0.05	0.82 (0.71–0.95)	<0.01
Duration of disease	non-early RA	18.1	68.2	Ref		Ref	
	early RA	25.7	80.0	1.42 (0.93–2.19)	0.11	1.18 (1.03–1.34)	<0.01
Nutritional status	normal weight	20.7	65.0	Ref		Ref	
	overweight/obesity	18.6	72.6	0.90 (0.66–1.22)	0.48	1.11 (1.00–1.24)	<0.05
eGFR	$\geq$ 60 mL/min/1.73 m <sup>2</sup>	18.2	69.8	Ref.		Ref.	
	<60 mL/min/1.73 m <sup>2</sup>	12.0	68.0	0.72 (0.25–2.08)	0.54	0.97 (0.74–1.27)	0.83

OR – odds ratio; eGFR – estimated glomerular filtration rate.



## Adverse drug reactions

In the period from initiation of Metex<sup>®</sup> use up to the 1<sup>st</sup> visit and the subsequent 160 days of follow-up, ADRs were reported in 16 patients (2.1%): nausea (n = 8; 1.0%), headache (n = 3; 0.4%), alopecia (n = 3; 0.4%), loose stools (n = 1; 0.1%), and injection site reaction (n = 1; 0.1%). There were no serious or severe ADRs, or reactions not included in the summary of product characteristics (SPC). As a consequence of ADRs, therapy with Metex<sup>®</sup> was discontinued in 6 patients, and doses applied were reduced in 2 patients. An at least 2-fold increase in ALT activity was observed in 10 patients (1.3%).

## Discussion

The results of the study confirmed the role of MTX as an anchor drug for patients with RA and are in agreement to numerous previous studies showing the efficacy and good tolerability of this drug. Unfortunately, the majority of these studies utilized oral MTX in monotherapy or in combination with other synthetic DMARDs and biologic agents, so the final conclusion on the therapeutic potential of MTX may not be free of bias. However, when we extracted data on sMTX administration from completed trials, they were in high concordance with those obtained in our study. During the 25–31 weeks of active treatment (including a 2–8 week period of MTX treatment before formal inclusion into the study) complete remission was obtained in 19.2% patients. This is in agreement with the results of Bijlsma et al.,<sup>9</sup> where the remission ratio in the sMTX arm was as high as 20% in week 20 followed by 40% and 44% in week 40 and 104, respectively. Quite recently, Müller et al.<sup>10</sup> published an analysis on the effectiveness of sMTX in patients with early RA from the St. Gallen RA cohort. This real-world analysis showed higher rates of remission (75.7%) and low disease activity (81.1%) than our study. However, some differences between these studies need to be addressed. The St. Gallen cohort comprised only patients with early RA (n = 70), in whom the remission rate is usually higher than in patients with long-lasting disease.<sup>10</sup> Moreover, as many as 37 of the patients from the analyzed cohort had been switched to biologic therapy due to the lack of MTX effectiveness.<sup>10</sup> After recalculation, the rate of clinical response to the achievement of low disease activity is about 40%, which is in agreement with our data.

The Treatment of Early Aggressive Rheumatoid Arthritis (TEAR) study was designed to assess the need for combination therapy in patients initially treated with MTX, and enrolled 775 patients with early RA.<sup>11</sup> In that study, 28% of patients treated with MTX had remission (DAS28 ≤ 2.6) at week 24, which is a slightly better result in comparison to our study, with remission attained in 19.2% of patients. The inclusion of selected patients with early RA may explain the higher rate of clinical response than in our study.

However, when we analyzed the data from a subgroup of patients with early RA, the results from both studies showed a similar effectiveness of MTX (25.7% in early RA in our study). The better clinical response in early RA (defined in our study as clinically overt disease duration of less than 6 months) than in patients with long-term disease shown in our study (OR = 1.18 (95% CI = 1.03–1.34)) is similar to that reported in a Swedish cohort where remission was observed in 30% patients on MTX monotherapy.<sup>12</sup> This is an important finding, as a relatively high clinical response rate in early RA in MTX monotherapy contributes significantly to the substantial reduction of disease-associated joint damage and overall better prognosis in line with the philosophy of the “opportunity window”. The efficacy of MTX in early RA can be seen in clinical trials with numerous biological agents where MTX served as the comparator. In one of them, the ACR 70 response index (roughly equal to remission in EULAR) in MTX alone reached the level of 20–25%,<sup>13</sup> which is again in perfect line with results from our study. The weak point of this comparison, however, is a lack of the specification of what route of administration was used in patients in these trials.

The high remission and low disease activity ratio observed in the current study (53.4% of patients) and the good clinical response observed in 69.5% of them may be explained by rapid titrating of MTX dose on the basis of clinical assessment during control visits, resulting in the increase in mean MTX dose by 2.2 mg per week. This indicates the need for detailed routine assessment of patients and for adjustment of the drug dose to obtain better clinical outcomes. In the present study, patients received relatively high MTX doses (20.2 ± 4.2 mg). It is known that the bioavailability of greater MTX doses (over 15 mg) differs depending on the route of administration. The bioavailability of oral MTX administration reaches a plateau for doses over 15 mg, whereas the bioavailability of sMTX shows further linear absorption.<sup>14</sup> This easily translates to better clinical response and a lower DAS index in patients on sMTX treatment, as was shown recently in early RA.<sup>15</sup> The superiority of sMTX over oral MTX was shown by Braun et al.<sup>16</sup> in a phase IV randomized double-blinded trial. This corresponds to the satisfactory response in our study that has been attained in a relatively high percentage of patients. There is also growing evidence that subcutaneous administration is superior to oral MTX in regard to its effectiveness and toxicity.<sup>15</sup>

It should be stressed that 1/3 of patients on sMTX in our study did not experience any clinical response. Such patients may benefit from switching to biologic agents; however, before the initiation of such therapy, combined treatment, including glucocorticosteroids, and MTX dose adjustment, especially in the patients without risk factors for the progressive disease, should be considered.<sup>3,7</sup>

Our study demonstrates a high adherence to sMTX therapy, with only 1% non-compliant patients. Similar data comes from 2 retrospective studies, where a higher rate

of therapy persistence in patients on sMTX than those receiving the drug orally has been observed.<sup>15,17</sup> There are several factors that may explain such good results. Firstly, sMTX is characterized by better tolerance and fewer ADRs. Secondly, the good clinical response and reduction of disease-associated symptoms observed in the majority of our patients contribute significantly to the very high continuation rate.

It is estimated that as many as 66% of patients on oral MTX experience adverse events, usually of low or moderate intensity, and in approx. ½ of the cases, the adverse events are related to the drug (ADRs). The most common ADRs reported in patients on MTX are gastrointestinal disturbances (nausea, vomiting, loss of appetite, and diarrhea).<sup>18</sup> Their occurrence precludes obtaining clinical benefits of MTX therapy. However, several reports emphasize that the frequency of ADRs may be reduced by choosing the subcutaneous route of administration.<sup>19,20</sup>

In addition, we showed a better response to MTX in overweight and obese patients. This is not surprising, as nutritional status somehow reflects the activity of the disease.<sup>21</sup> The rapid reduction of body weight in patients with RA is largely due to the release of pro-inflammatory cytokines (mainly but not exclusively to tumor necrosis factor  $\alpha$  (TNF- $\alpha$ )). Such an explanation of the relation between response to MTX and nutritional status does not seem to be fully justified, as we failed to find an association between RA activity and nutritional status assessed at the 1<sup>st</sup> visit.

The study showed the high efficacy and tolerance of sMTX in a real-world rheumatological practice and confirmed observations from heretofore completed controlled trials. The good efficacy of sMTX and low frequency of ADRs, which were only or mostly moderate and acceptable by the patients and did not cause therapy cessation in the study, seems to increase the adherence to the therapy by satisfied patients. During follow-up, including an earlier 2–8 week initial treatment period and subsequent 23 weeks of Metex<sup>®</sup> use, only 16 ADRs were reported. The most common ADR were: nausea (occurring in 1% of patients), alopecia (0.4%) and headache (0.4%). There were no ADRs not included in the SPC, nor were there serious or severe ADRs. As a consequence of ADRs, Metex<sup>®</sup> therapy was stopped in 6 patients, and in 2 patients the dose was reduced. Reported laboratory results show a more than 2-fold increase in ALT in 1.3% of patients only. However, the limited scope of the collected data does not allow a full interpretation of the results of the laboratory tests, and an explanation of the reasons for the increase in ALT and not reporting it as an ADR. In some cases, it may have been coexisting liver disease, concomitant use of statin or alcohol intake.

This study has some limitations related to the lack of data concerning therapy previously used, including other DMARDs and corticosteroids. The activity of RA was monitored with 2 DAS28 scoring systems with good clinical correlation, but not equivalence.<sup>8</sup>

## Conclusions

After 6-month therapy with sMTX, about 70% of patients with RA achieved a clinical response and remission was observed in 20%. Younger age, overweight/obesity and an early form of the disease are factors increasing therapy effectiveness. Subcutaneous MTX is well tolerated.

## References

- Alamanos Y, Voulgari PV, Drosos AA. Incidence and prevalence of rheumatoid arthritis, based on the 1987 American College of Rheumatology criteria: A systematic review. *Semin Arthritis Rheum.* 2006;36(3):182–188.
- Verschueren P, De CD, Corluy L, et al. Methotrexate in combination with other DMARDs is not superior to methotrexate alone for remission induction with moderate-to-high-dose glucocorticoid bridging in early rheumatoid arthritis after 16 weeks of treatment: The CareRA trial. *Ann Rheum Dis.* 2015;74(1):27–34.
- Smolen JS, Landewe R, Breedveld FC, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2013 update. *Ann Rheum Dis.* 2014;73(3):492–509.
- Singh JA, Saag KG, Bridges SL Jr, et al. 2015 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis. *Arthritis Rheumatol.* 2016;68(1):1–26.
- Smolen JS, Breedveld FC, Burmester GR, et al. Treating rheumatoid arthritis to target: 2014 update of the recommendations of an international task force. *Ann Rheum Dis.* 2016;75(1):3–15.
- Quinn MA, Emery P. Window of opportunity in early rheumatoid arthritis: Possibility of altering the disease process with early intervention. *Clin Exp Rheumatol.* 2003;21(5:Suppl 31):Suppl-7.
- Aletaha D, Neogi T, Silman AJ, et al. 2010 Rheumatoid arthritis classification criteria: An American College of Rheumatology/European League Against Rheumatism collaborative initiative. *Arthritis Rheum.* 2010;62(9):2569–2581.
- Sheehy C, Evans V, Hasthorpe H, Mukhtyar C. Revising DAS28 scores for remission in rheumatoid arthritis. *Clin Rheumatol.* 2014;33(2):269–272.
- Bijlsma JW, Welsing PM, Woodworth TG, et al. Early rheumatoid arthritis treated with tocilizumab, methotrexate, or their combination (U-Act-Early): A multicentre, randomised, double-blind, double-dummy, strategy trial. *Lancet.* 2016;388(10042):343–355.
- Muller RB, von KJ, Haile SR, Schiff MH. Effectiveness, tolerability, and safety of subcutaneous methotrexate in early rheumatoid arthritis: A retrospective analysis of real-world data from the St. Gallen cohort. *Semin Arthritis Rheum.* 2015;45(1):28–34.
- Moreland LW, O'Dell JR, Paulus HE, et al. A randomized comparative effectiveness study of oral triple therapy versus etanercept plus methotrexate in early aggressive rheumatoid arthritis: The treatment of Early Aggressive Rheumatoid Arthritis Trial. *Arthritis Rheum.* 2012; 64(9):2824–2835.
- van Vollenhoven RF, Ernestam S, Geborek P, et al. Addition of infliximab compared with addition of sulfasalazine and hydroxychloroquine to methotrexate in patients with early rheumatoid arthritis (Swefot trial): 1-year results of a randomised trial. *Lancet.* 2009; 374(9688):459–466.
- Smolen JS, Aletaha D. Rheumatoid arthritis therapy reappraisal: Strategies, opportunities and challenges. *Nat Rev Rheumatol.* 2015;11(5): 276–289.
- Schiff MH, Jaffe JS, Freundlich B. Head-to-head, randomised, cross-over study of oral versus subcutaneous methotrexate in patients with rheumatoid arthritis: Drug-exposure limitations of oral methotrexate at doses  $\geq 15$  mg may be overcome with subcutaneous administration. *Ann Rheum Dis.* 2014;73(8):1549–1551.
- Hazlewood GS, Thorne JC, Pope JE, et al. The comparative effectiveness of oral versus subcutaneous methotrexate for the treatment of early rheumatoid arthritis. *Ann Rheum Dis.* 2016;75(6):1003–1008.
- Braun J, Kastner P, Flaxenberg P, et al. Comparison of the clinical efficacy and safety of subcutaneous versus oral administration of methotrexate in patients with active rheumatoid arthritis: Results of a six-month, multicenter, randomized, double-blind, controlled, phase IV trial. *Arthritis Rheum.* 2008;58(1):73–81.

17. Scott DG, Claydon P, Ellis C. Retrospective evaluation of continuation rates following a switch to subcutaneous methotrexate in rheumatoid arthritis patients failing to respond to or tolerate oral methotrexate: The MENTOR study. *Scand J Rheumatol*. 2014;43(6):470–476.
18. Borchers AT, Keen CL, Cheema GS, Gershwin ME. The use of methotrexate in rheumatoid arthritis. *Semin Arthritis Rheum*. 2004;34(1):465–483.
19. Kromann CB, Lage-Hansen PR, Koefoed M, Jemec GB. Does switching from oral to subcutaneous administration of methotrexate influence on patient reported gastro-intestinal adverse effects? *J Dermatolog Treat*. 2015;26(2):188–190.
20. Hameed B, Jones H. Subcutaneous methotrexate is well tolerated and superior to oral methotrexate in the treatment of rheumatoid arthritis. *Int J Rheum Dis*. 2010;13(4):e83–e84.
21. Stavropoulos-Kalinoglou A, Metsios GS, Panoulas VF, et al. Underweight and obese states both associate with worse disease activity and physical function in patients with established rheumatoid arthritis. *Clin Rheumatol*. 2009;28(4):439–444.