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# Oral vs. subcutaneous low-dose methotrexate treatment in reducing gastrointestinal side effects

## *Rola doustnej bądź podskórnej drogi podania małych dawek metotreksatu w redukcji objawów niepożądanych ze strony układu pokarmowego*

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**Key words:** oral, subcutaneous methotrexate, intensity of gastrointestinal side effects.

**Słowa kluczowe:** doustny, podskórny metotreksat, nasilenie objawów niepożądanych ze strony układu pokarmowego.

**Summary**

The aim of our present data was to compare the gastrological side effects of oral versus subcutaneous (SC) administration of methotrexate in patients with long-lasting rheumatoid arthritis (RA). We compared the intensity of gastrological side effects such as nausea, vomiting, loss of appetite, abdominal pain and diarrhea in patients who received methotrexate (MTX) in oral or subcutaneous doses of either 7.5 mg or 15 mg weekly.

The survey research was used to evaluate the intensity of the above-mentioned side effects. The questionnaires were completed by a doctor, who conducted a structured interview with patients.

Patients receiving oral MTX had more intense gastrological side effects. There was a correlation between dose of oral MTX and intensity of side effects. Patients receiving 15 mg MTX orally had significant severe vomiting and loss of appetite ($p < 0.05$).

Nausea and loss of appetite turned out to be the most frequent side effects in patients receiving SC MTX 15 mg/weekly. In contrast to patients from the oral MTX groups none from the SC MTX groups exhibited vomiting or diarrhea.

We found that SC MTX administration demonstrated a significant reduction of gastrological side effects' intensity compared with oral administration of the same MTX dosage among patients with long-lasting RA.

**Streszczenie**

Celem pracy było porównanie objawów niepożądanych ze strony układu pokarmowego u pacjentów chorych na reumatoidalne zapalenie stawów (RZS), z długoletnim okresem trwania choroby, leczonych doustnie bądź podskórnie metotreksatem (MTX). Na podstawie badania ankietowego, z wywiadu od lekarza, porównywano częstość występowania nudności, wymiotów, utraty łaknienia, bólów brzucha i biegunek u pacjentów leczonych doustnie bądź podskórnie MTX w dawce 7,5 mg lub 15 mg/tydzień. U pacjentów otrzymujących MTX doustnie stwierdzono większe nasilenie objawów niepożądanych. Intensywność objawów korelowała z dawką MTX podawanego doustnie. W grupie chorych otrzymujących MTX doustnie znamiennie częściej występowały wymioty i utrata łaknienia ($p < 0,05$). Wśród chorych otrzymujących MTX podskórnie nudności i utratę łaknienia obserwowano częściej w grupie chorych otrzymujących metotreksat w dawce 15 mg.

W przeciwieństwie do chorych stosujących MTX doustnie u żadnego z chorych otrzymujących MTX podskórnie nie stwierdzono wymiotów i biegunek. Uzyskane dane wskazują na lepszą tolerancję MTX podawanego podskórnie w porównaniu z MTX stosowanym doustnie u pacjentów z długoletnim czasem trwania RZS. W grupie pacjentów otrzymujących MTX podskórnie u 14,6% stwierdzono również możliwość zmniejszenia o 50%

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We also observed the possibility of dosage reduction of other DMARDs. Using SC MTX therapy allowed 50% oral dosage reduction in 14.6% of patients among patients who received them.

dawek innych leków modyfikujących przebieg choroby (DMARD) podawanych równocześnie.

Methotrexate (MTX) remains the most widely prescribed of the disease-modifying anti-rheumatic drugs (DMARDs) and in general, MTX is well tolerated, but its clinical benefit is often limited by gastrointestinal side-effects [1]. Other possible side effects can include anaemia, neutropenia, increased risk of bruising and dermatitis. A small percentage of patients develop hepatitis, and there is an increased risk of pulmonary fibrosis.

MTX appears to be equal or superior to other disease-modifying agents and shows the best efficacy/toxicity tradeoffs [2-4]. Therefore, MTX is presented as a gold standard treatment and excellent disease-modifying drug for a whole host of rheumatic diseases – especially rheumatoid arthritis. Lower doses of methotrexate have also been shown to be very effective for the management of Crohn's disease and psoriasis.

The parenteral route is well tolerated and there are no significant differences in bioavailability between MTX administered subcutaneously (SC) and intramuscularly (IM), making the two routes interchangeable, but SC administration seems to be a more convenient and less painful way of administering low-dose MTX [5].

MTX acts by inhibiting the metabolism of folic acid and in cases of rheumatoid arthritis inhibition of dihydrofolate reductase (DHFR) is not thought to be the main mechanism, but rather the inhibition of enzymes involved in purine metabolism, leading to accumulation of adenosine, or the inhibition of T cell activation and suppression of intercellular adhesion molecule expression by T cells [6].

The aim of our present data was a comparison of the gastrological side effects of oral versus subcutaneous (SC) administration of methotrexate in patients with long-lasting rheumatoid arthritis (RA).

Our data are part of large, long-term clinical trials, which have been conducted in our Institute, related to treatment with oral versus subcutaneous MTX in patients with long and short lasting RA.

## Material and methods

We compared the side effects of subcutaneous methotrexate (SC MTX) with oral administration of methotrexate (MTX) therapy and evaluated obtained results. The gastrointestinal side effects such as nausea, vomiting, loss of appetite, abdominal pain and diarrhea were taken into consideration.

The survey research was used to evaluate the intensity of the above-mentioned side effects. The questionnaires were completed by a doctor, who conducted a structured interview with patients.

Our study involved 70 patients who suffered from long-lasting rheumatoid arthritis and were treated with SC MTX followed by oral MTX.

The patients who took part in the study had received treatment with oral MTX in 7.5 or 15 mg/weekly doses. Due to the mentioned side effects, they were respectively switched to 7.5 or 15 mg/weekly SC MTX doses. In consequence, every patient received the same dose of MTX either orally or subcutaneously.

Among the 70 treated patients only 41 patients had, in addition, been taking one of the two disease-modifying antirheumatic drugs such as sulphasalazine and leflunomide.

Questions no. 3 and 4 that referred to the evaluation of the side effects are based on the Likert response scale. If the patient responded in writing that he/she had no side effects it was reported as none (side effects) and described in the analysis as 0. If the patient assessed the side effects as moderate/ /weak/slight, that was reported as moderate (side effects) and described in the analysis as 2. If the patient described the side effects as strong/severe, that was reported as strong (side effects) and analyzed as 4.

The presented questionnaire is part of a survey that researches the effectiveness of MTX treatment. The survey is being conducted on a more significant number of patients.

Data were coded, categorized and analyzed using a one- and a multi-way analysis of variance (ANOVA). All statistical analyses were done with Statgraphics. A p-value less than 0.05 was considered as indicating a statistically significant relationship between the variables at 99% confidence level. Data are expressed as mean ± SD (standard deviation of the mean).

The study was approved by the Institute Ethical Committee and informed consent was obtained from the patients.

Data were coded, categorized and analyzed using Statgraphics and ANOVA and SPSS 14.0 for Windows (SPSS Inc., Chicago, IL, USA). The incidence of therapy discontinuation and the reason for discontinuation were noted.

## Results

Seventy patients were included in the study, all of them receiving oral MTX before starting with SC MTX.

The time of treatment with oral MTX was a maximum of 24 months, mean 17.8 ±7.0 months.

The time of treatment with SC MTX was a maximum of 24 months, mean 7.3 ±4.2 months.

The study population consisted of 70 patients (64 women, 6 men) with a mean age of 55 ±14 years and with a primary diagnosis of rheumatoid arthritis whose mean duration was 11.5 ±6.2 years.

We compared the intensity of gastrological side effects such as nausea, vomiting, loss of appetite, abdominal pain, and diarrhea in patients who received MTX in doses of either 7.5 mg or 15 mg, orally or subcutaneously.

Patients receiving oral MTX had more intense gastrological side effects. There was a correlation between dose of oral MTX and intensity of side effects. Patients receiving 15 mg MTX orally had significant severe vomiting and loss of appetite ($p < 0.05$) (Fig. 1).

Nausea and loss of appetite turned out to be the most frequent side effects in patients receiving SC MTX 15 mg/weekly. In contrast to patients from the oral MTX groups none from the SC MTX groups exhibited vomiting or diarrhea (Fig. 2).

We found that intensity of gastrointestinal side effects was dependent on both dose and ways of giving MTX. The patients receiving treatment with SC MTX had less intense side effects such as nausea and abdominal pain (Fig. 3, Fig. 4).

## Discussion

The results of our study show that when the way of MTX administration is switched from oral to subcutaneous form it allows us to reduce intensity of gastrointestinal side effects in all enrolled patients. We would also like to stress that in contrast to other authors [7-10] we evaluated intensity of gastrointestinal side effects and not their prevalence solely, which directly affects patients' quality of life. A very interesting article by Prof. Braun et al. demonstrated a comparison of oral MTX and subcutaneous MTX in relation to efficacy, safety and tolerability [11]. Our study differs from Prof. Braun's study in several aspects. First of all, the patients taking part in our study have suffered from rheumatoid arthritis for many years; secondly, in both groups of patients the doses of MTX were the same, so each patient received the same dose orally or subcutaneously. Furthermore, in our patients other DMARDs were administered simultaneously; and finally, our time of observation was longer than the period presented in Prof. Braun's study. We did not find any available clinical

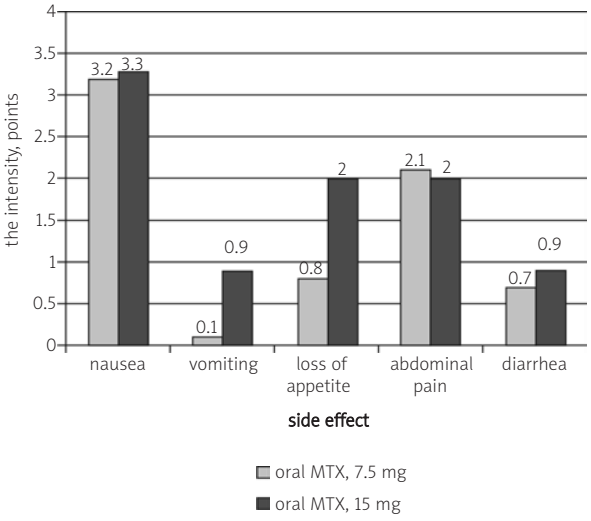


**Fig. 1.** Intensity of gastrointestinal side effects in patients received oral MTX in doses of 7.5 or 15 mg.
***Ryc. 1.*** *Nasilenie objawów ubocznych ze strony przewodu pokarmowego u pacjentów przyjmujących MTX doustnie w dawce 7.5 bądź 15 mg.*

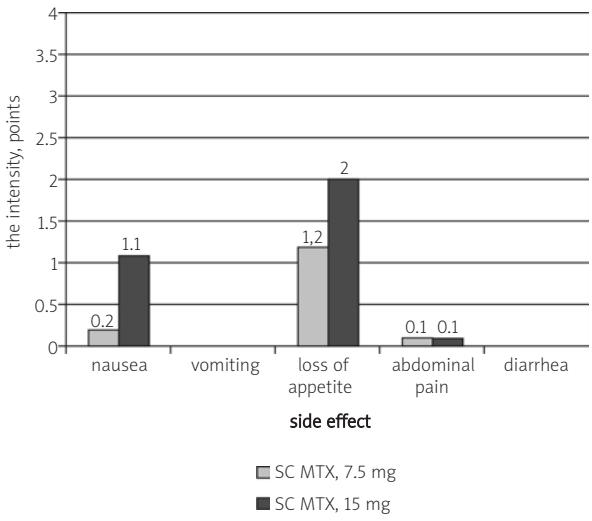


**Fig. 2.** Intensity of gastrointestinal side effects in patients received subcutaneous MTX in doses of 7.5 or 15 mg.
***Ryc. 2.*** *Nasilenie objawów ubocznych ze strony przewodu pokarmowego u pacjentów przyjmujących MTX podskórnie w dawce 7.5 bądź 15 mg.*

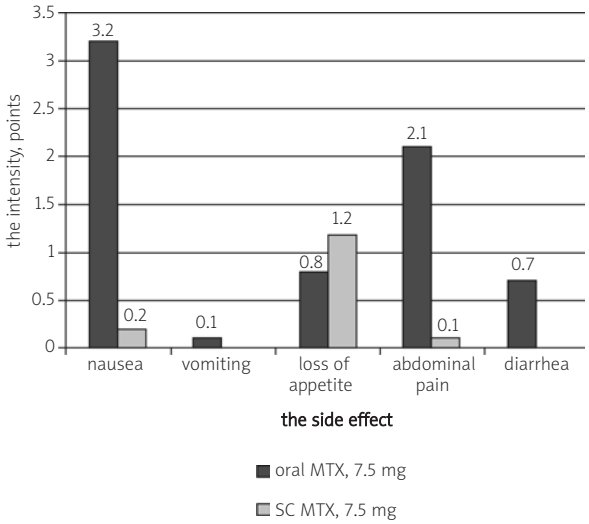


**Fig. 3.** Intensity of gastrointestinal side effects in patients received oral or subcutaneous MTX in dose 7.5 mg

***Ryc. 3.*** *Nasilenie objawów ubocznych ze strony przewodu pokarmowego u pacjentów przyjmujących MTX doustnie bądź podskórnie w dawce 7.5 mg*

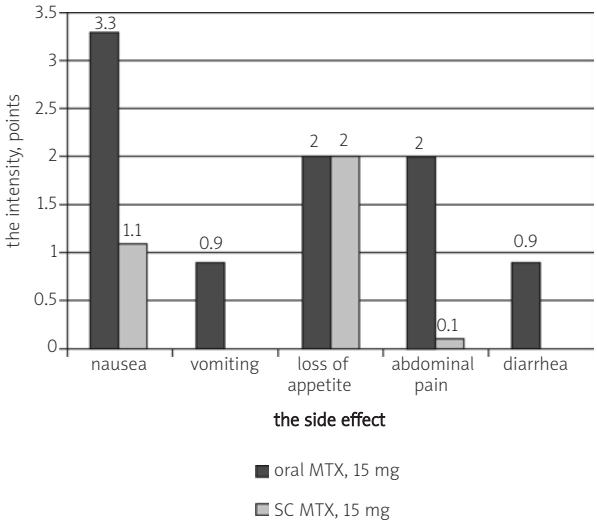


**Fig. 4.** Intensity of gastrointestinal side effects in patients received oral or subcutaneous MTX in dose 15 mg.

***Ryc. 4.*** *Nasilenie objawów ubocznych ze strony przewodu pokarmowego u pacjentów przyjmujących MTX doustnie bądź podskórnie w dawce 15 mg.*

data concerning intensity of gastrointestinal side effects during treatment with MTX. Moreover, mean time of observation was longer in our study in comparison to Braun's study and was 17.8 months for oral MTX and 7.3 months for subcutaneous MTX, which makes our data reliable and credible as well. We can say that our data have demonstrated that switching from oral to subcutaneous MTX allowed the dose-independent intensity of nausea and abdominal pain to be reduced (Fig. 1, 2). There was no difference in intensity of loss of appetite in patients who received 15 mg MTX orally or subcutaneously (Fig. 4). In contrast to these patients, the patients who received 7.5 mg SC MTX presented higher intensity of loss of appetite than those patients taking 7.5 mg MTX orally (Fig. 3). Additionally, subcutaneously given MTX allowed us to eliminate such gastrointestinal side effects as vomiting and diarrhea. We did not find in the literature any data concerning these aspects. We have only found the study presented by Wegrzyn et al. which related to tolerance to MTX in patients with rheumatoid arthritis who were switched from intramuscular to oral administration [12]. The authors observed a greater frequency of gastrointestinal symptoms when methotrexate was switched from intramuscular to oral administration. A similar observation was made by Świerkot et al. [13].

Finally, we would like to point out that according to our observations it is possible to reduce the dose of DMARDs which are given together with SC MTX. As this result has been achieved with only a few patients (14%) further conclusions on this aspect ought to be evaluated and confirmed in other studies. Nevertheless, so far we have not found studies related to this problem and we suggest that this report needs more studies for confirmation.

In conclusion, we found that efficacy of SC MTX administration demonstrated a significant reduction of gastrological side effects' intensity compared with oral administration of the same MTX dosage among patients with long-lasting RA.

We also observed the possibility of dosage reduction of other drugs such as DMARDs. Using SC MTX therapy allowed 50% oral dosage reduction in 14.6% of patients among patients who received them.

The authors have declared no conflicts of interest.

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