Methotrexate treatment for rheumatoid arthritis in Poland: Retrospective analysis of patients in routine clinical practice

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Abstract

Objectives: The aim of this study was to evaluate methotrexate (MTX) treatment administered by Polish rheumatologists in everyday practice.

Material and methods: The study was based on a retrospective analysis of a cohort of 1957 patients with rheumatoid arthritis (RA). It was conducted among 100 rheumatologists, each of whom received 20 questionnaires and completed them based on the data from their rheumatoid arthritis patients.

Results: Methotrexate was taken by 91% of patients, and 80% of them continued the treatment either as a monotherapy (65%) or concomitantly with other disease-modifying anti-rheumatic drugs. In 60% of the cases, therapy was initiated within six months of diagnosis. Dose modifications were observed in 76% of cases and were contingent on different factors, e.g. lack of efficacy, presence of adverse events. The most prevalent adverse events were nausea and vomiting, weakness, and elevated liver enzyme activity. The most common initial dose of MTX was 10 or 15 mg/week. An increase in dose to the maximum of 25 mg/week was observed in 36% of cases, with continuation for 27% of patients. Treatment interruption was noted in 21% of patients, predominantly due to MTX intolerance; however, in 13% of cases, it was due to patient choice.

Conclusions: Methotrexate is the most common agent used to treat rheumatoid arthritis. Dose modifications are often applied to maximise efficacy and reduce adverse reactions, which could lead to withdrawal. Methotrexate is an effective drug for treatment of RA when used according to current recommendations. To optimise MTX therapy, regular medical visits are required.

Key words: methotrexate, rheumatoid arthritis, everyday practice, treatment.

Introduction

The goal of rheumatoid arthritis (RA) therapy is to obtain remission or low disease activity. According to the guidelines of all major rheumatological associations (European League Against Rheumatism [EULAR], American College of Rheumatology [ACR]), treatment with a synthetic disease-modifying antirheumatic drug (sDMARD) should be initiated as soon as possible after disease diagnosis [1–3]. Rheumatoid arthritis treatment plans should be based on a mutual decision between patient and rheumatologist. It is evident that more physicians acknowledge the necessity for a change in treatment therapy due to the shortened time frame between the diagnosis and disease-modifying antirheumatic drug (DMARD) administration from 120 months in 1965, to 30 months in 1975, five months in 1985, and zero to two months presently. For the past 20 years, the main sDMARD used in clinical practice has been methotrexate (MTX). Recommendations on the administration of MTX in everyday practice have been published in several articles [1, 4–6]. Methotrexate should be rapidly escalated, usually to

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25–30 mg/week, orally or subcutaneously administered, with folic acid supplementation, and the maximal MTX dose, if tolerated, should be sustained for about 8–12 weeks to judge the MTX treatment response [1, 7].

Remission or at least low disease activity should be obtained within six months, and at least 50% clinical improvement within three months is desirable. If therapeutic goals are not accomplished with the first line of treatment and there are poor prognostic factors, the possibility of adding a biological agent to treatment should be considered. The importance of MTX therapy in the treatment of RA is clear, despite the introduction of new biological agents for RA treatment. New biological agents should be used together with MTX if there are no contraindications [1–3, 5–8]. Methotrexate is currently administered to over 500,000 rheumatoid arthritis patients worldwide. A good response to treatment is obtained in 35% to 65% of patients, and in 10% to 30% of patients treatment is discontinued due to adverse events.

Table I. Time of MTX initiation and duration of MTX therapy

| Duration of MTX therapy (in months) | Patients |
|-------------------------------------|----------|
| 0–2                                 | 4.4%     |
| 3–6                                 | 7.5%     |
| 7–12                                | 8%       |
| 13–24                               | 17.4%    |
| 25–60                               | 32%      |
| 61–96                               | 14%      |
| 97–180                              | 11.5%    |
| > 180                               | 2.7%     |
| No answer to the question           | 2.5%     |
| Average in months                   | 51.3     |
| Median in months (min.–max.)        | 35.6 (1–364) |

| Time elapsed from time of diagnosis to MTX treatment initiation (in months) | Patients |
|-----------------------------------------------------------------------------|----------|
| 0 (at the time of diagnosis)                                                | 45%      |
| 1–6                                                                         | 15%      |
| 7–24                                                                        | 10%      |
| 25–60                                                                       | 11%      |
| 61–120                                                                      | 8%       |
| > 120                                                                       | 7%       |
| No answer to the question                                                   | 4%       |
| Average in months                                                           | 29.2     |
| Median in months (min.–max.)                                                | 0.49 (0–571) |

The aim of this study was to evaluate MTX treatment administered by Polish rheumatologists in everyday practice.

Material and methods

The study was conducted among 100 rheumatologists from different centres across Poland, which were chosen to reflect the current global structure of RA treatment in Poland. During sample selection a percentage distribution of rheumatologists in every region was used, which was calculated based on the data from the Polish Chamber of Physicians. Every physician obtained 20 questionnaires that were supposed to be filled out during the next 20 visits of patients with RA. The questionnaires were filled out after each visit based on medical records and patient history. Besides questions regarding general patient information, the diagnostic process, and administered treatment, the questionnaire also included detailed questions about MTX treatment. These questions pertained to the start date and end date of treatment, evaluation of disease activity, and doses of the administered drug including the maximal dose and the dose at the beginning of treatment. The questionnaire requested detailed information regarding any dose modifications and the reasons for them, adverse events, and reasons for discontinuing MTX administration. Ethical approval and informed consent (according to the Declaration of Helsinki) was obtained.

Results

Sample characteristics

A total of 100 rheumatologists participated in the study by completing questionnaires regarding their RA patients, and a total of 1957 questionnaires were collected. Among the patients treated with MTX, 79% were women and the median age was 58.1 years.

Methotrexate use

Patients who had taken MTX at any time constituted 91% of all the examined patients (1781), and in 61% of them MTX was the first sDMARD used. At the time of filling out the questionnaires, 80% of all the patients were still taking MTX. Of those patients still taking MTX, 81% were taking it as monotherapy, 16.2% were taking it in combination therapy with another sDMARD, and 2.8% were taking it in combination therapy with a biological agent. The mean duration of MTX administration among the examined patients was 51.3 months (median 35.6 months). Patients who took MTX for less than three months constituted 4.4% of patients who had taken MTX at any time. The largest group consisted of patients...
taking MTX from two to five years (32%) (Table I). The last dose of MTX was administered orally in 82% of patients and subcutaneously in 18% of patients who had taken MTX at any time.

Methotrexate was used as a first-line therapy in 75% of patients with the disease for up to one year. The median duration from the time of diagnosis to initiation of MTX therapy was not even half a month (0.49 month) for all patients who had taken MTX at any time (Table I).

### Treatment interruption

Methotrexate treatment was interrupted in 21% of all patients who had taken MTX at any time. The most common reasons were gastrointestinal adverse events, treatment contraindications, or patient choice (Table II). Depending on the length of MTX therapy, other reasons for treatment discontinuation were observed. For example, for patients who had taken MTX for one to two years or 10 to 15 years, infection was the reason for treatment discontinuation in 17% and 20% of patients, respectively. The risk of permanent discontinuation of MTX treatment increased together with duration of treatment (in patients who used MTX for up to six months, it was present in less than 10%; in patients treated for over five years, it was present in 20%; and when treatment was administered for over eight years, it was present in one-third of the patients). Between the 7th and 12th month of MTX treatment, the main reason for discontinuation of treatment was drug intolerance (44%) or a patient choice (34%).

### Methotrexate dose

During treatment, MTX dose was modified in 76% of patients; the dose was decreased in 24% of these cases, increased in 61%, and both increased and decreased in 15%. The main reasons for dose reduction were adverse events and remission, whereas the main reason for dose increase was ineffective treatment. The adverse events leading to MTX dose modification were nausea and vomiting, malaise and general weakness, increased activity of liver enzymes, and hair loss (Table III). The average starting dose for MTX therapy was 13.4 mg/week (median 11.9 mg/week), whereas most commonly, treatment was started with 10 mg/week (in 36% of patients) or 15 mg/week (in 32% of patients). The average maximal dose obtained during treatment was 20.2 mg/week (median 19.3 mg/week). The most common dosages among patients that were currently taking MTX were 25 mg/week (27%), 20 mg/week (24%), and 15 mg/week (21%) (Table IV).

Subcutaneous MTX was used in 18% of patients. The last administered dose in these patients was usually 25 mg/week (46%), and the lowest dose of 15 mg/week was administered in only 6% of patients.

### Disease activity

At the time of MTX therapy initiation, patients were characterised with moderate or high disease activity. Most patients who were still using MTX at the time of the study had a lower number of painful and swollen joints in comparison to the beginning of their treatment. A similar situation is observed in regard to ESR and CRP, but more than a half of the patients still had elevated inflammatory markers.

### Effectiveness of treatment

According to EULAR guidelines, the RA treatment goal should be to obtain remission or to reduce disease
activity after three to six months. Therefore, to evaluate the effectiveness of RA treatment in Poland, a group of patients (101) who were treated from three to six months were selected. In more than a half of the patients (62%) remission or reduction of disease activity were diagnosed based on DAS-28. Patients with a moderate and high disease activity constituted 41% and 59%, respectively, at the moment of therapy initiation and 26% and 12%, respectively, after three to six months of MTX treatment (Table V).

Discussion

The results of this study show that over 90% of the observed RA patients have used MTX in the past. Methotrexate was the initial treatment as a monotherapy chosen by most rheumatologists, which is in accordance with the EULAR and ACR guidelines [1, 3]. The results of earlier research studies indicate that in selected groups of patients with a very active course of disease and risk factors indicating a fast progression of disease, it may be appropriate to administer more than one sDMARD in combination therapy as a first-line treatment [9].

It is important to start treatment with a sDMARD as soon as possible after RA diagnosis because this provides the highest probability to achieve remission [10]. In 60% of patients, MTX was administered in the first six months after the diagnosis of RA (in 45% immediately after the diagnosis), and the median duration from the moment of diagnosis to administration of MTX was approximately half a month. It would be interesting to evaluate the reasons why MTX was not administered immediately after diagnosis. We must acknowledge that some patients have contraindications to the use of MTX, and some patients do not accept or consent to MTX therapy due to fear and the risk of toxic adverse events. Continued education of the necessity for imme-

Table IV. Methotrexate dosing

| Doses of MTX (n = 1781, patients who had taken MTX at any time) | Starting treatment dose Patients (%) | Maximal dose obtained during treatment Patients (%) | Last administered dose Patients (%) |
|---------------------------------------------------------------|-------------------------------------|---------------------------------------------------|-----------------------------------|
| ≤ 7.5 mg/week                                                 | 8                                   | 2                                                 | 3                                 |
| 10 mg/week                                                    | 36                                  | 8                                                 | 13                                |
| 12.5 mg/week                                                  | 8                                   | 6                                                 | 7                                 |
| 15 mg/week                                                    | 31                                  | 14                                                | 21                                |
| 17.5                                                          | 1                                   | 1.5                                               | 2                                 |
| 20                                                            | 11                                  | 26                                                | 24                                |
| 22.5                                                          | 0                                   | 1.3                                               | 0.7                               |
| 25                                                            | 2                                   | 36                                                | 27                                |
| 27.5                                                          | 0                                   | 0.4                                               | 0.3                               |
| 30                                                            | 0                                   | 4                                                 | 1                                 |
| No answer                                                     | 3                                   | 0.8                                               | 1                                 |
| Average dose                                                  | 13.4 mg/week                        | 20.2 mg/week                                      | 18.2 mg/week                      |
| Median                                                        | 11.9 mg/week                        | 19.3 mg/week                                      | 17.9 mg/week                      |

Table V. Parameters evaluating disease activity before and after 3–6 months of MTX treatment

| Measured parameter | Patients taking MTX for 3–6 months |
|--------------------|------------------------------------|
|                    | At the beginning of therapy (n = 101) | After 3–6 months (n = 101) |
| Number of swollen joints ≥ 3 | 88 | 40 |
| Number of swollen joints ≤ 1 | 21 | 57 |
| Number of painful joints ≥ 3 | 99 | 52 |
| Number of painful joints ≤ 1 | 0.3 | 48 |
| ESR > 15 mm/h | 84 | 58 |
| DAS-28: ≤ 2.6 | 40 | 45 |
| 2.61–3.2 | 17 | 17 |
| 3.21–5.1 | 26 | 26 |
| > 5.1 | 12 | 12 |
Methotrexate treatment for rheumatoid arthritis in Poland

It is important to identify and understand factors leading to MTX treatment interruption. The most common (60%) reasons reported for treatment interruption in this study included adverse events, contraindications to MTX therapy, and planning a pregnancy. In the current study, the most common adverse events of MTX treatment were gastroenterological symptoms, nausea, dyspeptic symptoms, and abdominal pain. The profile and frequency of adverse events reported in the study questionnaire are in accordance with those described in the literature [16–19]. While these common adverse events can be associated with the administration of MTX, it is always important to take a thorough patient history to verify if they are not caused by other reasons such as administration of NSAIDs, dietary changes, or stress. If the observed adverse events are associated with oral MTX therapy, then subcutaneous MTX therapy should be attempted. It is also important to recognize the rare, but more dangerous complications of MTX treatment such as significant increase of aminotransferases, infections, and leukopenia. In the observed group, infections were diagnosed more commonly at the beginning of treatment or in patients with long-standing RA. These adverse events may be associated with a frequent one-time administration of glucocorticosteroids, and an older age in patients with long-standing RA. In most cases, there is no need for MTX dose modification when upper respiratory infections occur. But in cases of pneumonia, most authors recommend a temporary discontinuation of MTX [20]. Pneumavax vaccination should be administered in all RA patients, especially in older men with a history of lung disease [21].

Two of the most commonly reported adverse events were general weakness and malaise. The feeling of tiredness and general weakness can be caused by a discontinuation of MTX in up to 20% of patients who have stopped therapy [17]. Sometimes it is enough to divide the dose into two or three parts and administer it every 12 hours, to lower the MTX dose, or to administer MTX on a day off from work. Interestingly, drug intolerance was reported as the reason for treatment discontinuation in 31% of the women but in only 18% of the men. However, significantly more men discontinued treatment without previous agreement from the doctor than women (27% and 10%, respectively).

In current practice, significant emphasis is placed on the treatment decision-making process by the physician and patient together. Physicians should ensure that patients understand that MTX treatment has been shown to be associated with a 70% decrease in mortality among patients with RA and a lower mortality due to cardiovascular causes [22, 23]. After obtaining a remission, when glucocorticoids are no longer administered, a gradual lowering of the MTX dose can be considered, elongating the period between administered doses. However, MTX should not be discontinued abruptly.

Particular attention should be paid to patients between the 6th and 12th month of treatment. During that time, most patients discontinued MTX treatment because of drug intolerance (44%) or without previous agreement from their physician (34%). A problem that occurs after reaching the therapeutic goal is that it often discourages patients from continuing MTX treatment. In these cases, the physician’s role in therapy modification is crucial to prevent abrupt treatment discontinuation by the patient. Additionally, based on previous observa-
tions, there is no need for MTX discontinuation during the perioperative period. In the observed group, treatment was discontinued in 7% of cases.

Based on the data from the study survey, we observed favourable trends regarding the administration of appropriate MTX doses in patients with RA. Seventy-five per cent of rheumatologists recommended a starting dose between 10 mg and 15 mg once a week, which is the suggested dosing of most recommendations [1–3]. On average, it is recommended that the MTX dose be rapidly increased, usually to 25–30 mg/week, if therapeutic goals are not achieved and if there are no adverse events associated with MTX [1]. Approximately three-fourths of patients evaluated at their last visit had been given an MTX dose between 15 mg and 30 mg. It should be emphasised that by taking a chronic MTX dose of 30 mg every week, the monthly dose is 120 mg, and the yearly dose is 1440 mg. This is why laboratory tests (CBC, AST, ALT) must be routinely administered during therapy to identify possible adverse events. The correlation between the degree of liver fibrosis and the cumulative MTX dose together with the possibility of assessing the advancement of these changes in elastography are still debatable [24, 25]. The sensitivity of elastography in the early stages of fibrosis is 56% to 67% and specificity is 89% to 91%.

The approach of French rheumatologists seems to be appropriate; they observed the need to adjust MTX dose according to patient weight [2]. According to them, the appropriate MTX dose is 0.3 mg/kg/week. These recommendations, however, were not included in the latest EULAR recommendations [1]. In order to individualise patient therapy for best results, we should consider whether to administer a maximal dose of MTX, change the route of administration to subcutaneous, or add other sDMARD or biological agents.

Subcutaneous MTX was administered in almost one-fifth of the patients, indicating awareness among the survey physicians of this therapy option. The last administered doses of subcutaneous MTX were usually high (in 46% of patients it was 25 mg/week) which could indicate that the reason for changing the route of administration was due to ineffectiveness. The average dose was also higher for subcutaneous MTX than for oral (21 mg and 17 mg/week, respectively). Changing to subcutaneous administration should be considered when oral treatment is ineffective, when there is a failure to comply with recommendations, when there are gastrointestinal adverse events, or before the biological therapy, especially in the beginning of therapy.

Besides the administered dose, it is important to constantly adjust therapy to current disease activity and potential adverse events. Considering the data from the survey, it seems that most Polish physicians are aware of this. The MTX dose was modified in more than three-fourths of patients. The necessity for frequent follow-up visits should be emphasised, especially in the beginning of therapy.

When administered in accordance with current recommendations MTX is a safe drug, and its use is appropriate considering its effectiveness and adverse events [1, 3, 6]. Some studies have confirmed MTX therapy duration of over five years in 74% of patients, and at least 12 years in more than 50% of patients [30]. It is pleasing to see that more physicians and patients see the advantages of MTX use. The demonstrated advantages of MTX include:

- a higher percentage of patients continue long-term therapy with MTX when compared to other sDMARDs,
- MTX has a relatively short time from initiation of therapy to onset of therapeutic effects,
- MTX has a relatively low cost,
- MTX can be used in both monotherapy and combination therapy,
- increases the effectiveness of biological drugs,
- MTX has the best ratio of effectiveness/toxicity among all sDMARDs [4, 6, 7, 19].

Conclusions

1. Methotrexate is an effective drug for treatment of RA when used according to current recommendations.
2. Dose modifications of MTX are often applied to maximise efficacy and reduce adverse reactions, which could lead to withdrawal.
3. To optimise MTX therapy, regular medical visits are required.

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References

1. Smolen JS, Landewé R, Bijlsma J, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2016 update. Ann Rheum Dis 2017; 76: 960-977.
2. Gaujoux-Viala C, Gossec L, Cantagrel A, et al. Recommendations of the French Society for Rheumatology for managing rheumatoid arthritis. Joint Bone Spine 2014; 81: 287-297.
3. Singh JA, Saag KG, Bridges SL Jr, et al. 2015 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis. Arthritis Rheum 2016; 61: 1-26.
4. Visser K, Katchamart W, Loza E, et al. Multinational evidence-based recommendations for the use of methotrexate in rheumatic disorders with a focus on rheumatoid arthritis: integrating systematic literature research and expert opinion of a broad international panel of rheumatologists in the 3E Initiative. Ann Rheum Dis 2009; 68: 1086-1093.

5. Molina J. Recommendations for the Use of MTX in RA. Reumatol Clin 2015; 11: 3-8.

6. Bello AE, Perkins EL, Jay R, Efthimiou P. Recommendations for optimizing methotrexate treatment for patients with rheumatoid arthritis. Open Access Rheumatol 2017; 9: 67-79.

7. Tkac A, Paradowska-Gorycka A, Kwiatkowska B, Raciborski F. Personalized medicine in rheumatology. Reumatologia 2016; 54: 177-186.

8. Burmester GR, Pope JE. Novel treatment strategies in rheumatoid arthritis. Cochrane Database Syst Rev 2014; 10: CD000957.

9. Graudal N, Hubeck-Graudal T, Tarp S, et al. Effect of Combining Methotrexate with Hydroxychloroquine or Leflunomide in Rheumatoid Arthritis: A Systematic Review and Meta-Analysis. Semin Arthritis Rheum 2016; 45: 656-662.

10. Bakker MF, Jacobs JW, Welsing PM, et al. Early clinical response to treatment predicts 5-year outcome in RA patients: follow-up results from the CAMERA study. Ann Rheum Dis 2011; 70: 1099-1113.

11. NICE commissioning guides. Support for commissioning for rheumatoid arthritis [CMG51] 01 June 2013 http://www.nice.org.uk/guidance/cmg51.

12. Kulig M, Malec Z, Stustochowick W. Analiza leczenia ambulatoryjnego metotrexatem chorych na reumatoidalne zapalenie stawów. Reumatologia 2009; 47: 202-206.

13. Nikolaisen C, Kvien TK, Mikkelsen K, et al. Contemporary use of disease-modifying drugs in the management of patients with early rheumatoid arthritis in Norway. Scand J Rheumatol 2009; 19: 1-6.

14. Anderson JJ, Wells G, Verhoeven AC, Felson DT. Factors predicting response to treatment in rheumatoid arthritis: the importance of disease duration. Arthritis Rheum 2000; 43: 22-29.

15. Saevardsdottir S, Wallin H, Seddighzadeh M, et al. Predictors of response to methotrexate in early DMARD naïve rheumatoid arthritis: results from the initial open-label phase of the SWEFOT trial. Ann Rheum Dis 2011; 70: 469-475.

16. Świerkot J, Sokolik R, Gruszecka-Marczynska K, et al. Skuteczność leczenia i występowanie działań niepożądanych w trakcie terapii metotrexatem podawanym doustnie i podskórnie chorych na reumatoidalne zapalenie stawów. Reumatologia 2008; 46: 322-329.

17. Nikiforou E, Negoeescu A, Fitzpatrick JD, et al. Indispensable or intolerable? Methotrexate in patients with rheumatoid and psoriatic arthritis: a retrospective review of discontinuation rates from a large UK cohort. Clin Rheumatol 2014; 33: 609-614.

18. Curtis J, Bykerk V, Aassi M, Schiff M. Adherence and Persistence with Methotrexate in Rheumatoid Arthritis: A Systematic Review. J Rheumatol 2016; 43: 1997-2009.

19. Lopez-Ollvo MA, Siddhanamatha HR, Shea B, et al. Methotrexate for treating rheumatoid arthritis. Cochrane Database Syst Rev 2014; 10: CD000957.

20. Bogas M. Methotrexate treatment in rheumatoid arthritis. Clin Rheumatol 2010; 29: 629-635.

21. Coulson E, Saravanan V, Hamilton J, et al. Pneumococcal antibody levels after pneumovax in patients with rheumatoid arthritis on methotrexate. Ann Rheum Dis 2011; 70: 1289-1291.

22. Micha R. Systematic Review and Meta-Analysis of Methotrexate Use and Risk of Cardiovascular Disease. Am J Cardiol 2011; 108: 1362-1370.

23. Wasko MC, Dasgupta A, Hubert H, et al. Propensity-adjusted association of methotrexate use with overall survival in rheumatoid arthritis. Arthritis Rheum 2013; 65: 334-342.

24. Arena U, Stasi C, Mannori A, et al. Liver stiffness correlates with methotrexate cumulative dose in patients with rheumatoid arthritis. Dig Liver Dis 2012; 44: 149-153.

25. Rouhi A, Hazlewood G, Shafeen AA, et al. Prevalence and risk factors for liver fibrosis detected by transient elastography or shear wave elastography in inflammatory arthritis: a systematic review. Clin Exp Rheumatol 2017; 35: 1029-1036.

26. Fitzpatrick R, Scott DG, Keary I. Cost-minimisation analysis of subcutaneous methotrexate versus biologic therapy for the treatment of patients with rheumatoid arthritis who have had an insufficient response or intolerance to oral methotrexate. Clin Rheumatol 2013; 32: 1605-1612.

27. Rutkowska-Sak L, Reil-Bakalarska M, Lisowska B. Rola doustnej bądź podskórnej drogi podania małych dawek metotreksatu w redukcji objawów niepożądanych ze strony układu pokarmowego. Reumatologia 2009; 47: 207-211.

28. Li D, Yang Z, Kang P, Xie X. Subcutaneous administration of methotrexate at high doses makes a better performance in the treatment of rheumatoid arthritis compared with oral administration of methotrexate: A systematic review and meta-analysis. Semin Arthritis Rheum 2016; 45: 656-662.

29. Bianchi G, Caporali R, Todierti C, Mattana P. Methotrexate and rheumatoid arthritis: current evidence regarding subcutaneous versus oral routes of administration. Adv Ther 2016; 33: 369-378.

30. Wluka A, Buchbinder R, Mylvaganam A, et al. Long term methotrexate use in rheumatoid arthritis: 12 year follow up of 460 patients treated in community practice. J Rheumatol 2000; 27: 1864-1871.