Suboptimal methotrexate use in rheumatoid arthritis patients in Italy: the MARI study

L. Idolazzi[1], S. Adami[1], R. Capozza[2], G. Bianchi[3], A. Cozzolongo[4], O. Epis[5], E. Fusaro[6], G. Lapadula[7], A. Migliore[8], R. Pellerito[9], A. Pucino[10], L. Sinigaglia[11], E. Visalli[12], M. Rossini[1]

[1]Rheumatology, Department of Internal Medicine, Azienda Ospedaliera Universitaria Integrata, Verona; [2]Rheumatology, Ospedale CTO A. Alesini, ASL Roma C, Rome; [3]Rheumatology, Ospedale La Colletta, Arenzano, Genoa; [4]Rheumatology, Ospedale San Paolo, Bari; [5]Rheumatology, A.O. Ospedale Niguarda Ca' Granda, Milan; [6]Rheumatology, Azienda Ospedaliero-Universitaria S. Giovanni Battista, Turin; [7]Rheumatology, Ospedale Policlinico, Bari; [8]Rheumatology, Ospedale S. Pietro Fatebenefratelli, Rome; [9]Rheumatology, A.O. Ordine Mauriziano di Torino - ASL TO1, Turin; [10]Rheumatology, ASL Napoli 1 Centro Distretti 24 -27 -31, Naples; [11]Rheumatology, Azienda Ospedaliera Istituto Ortopedico G. Pini, Milan; [12]Rheumatology, A.O.U. Policlinico Universitario G. Martino, Messina, Italy.

Abstract

Objective

Methotrexate (MTX) is the first choice in the treatment of rheumatoid arthritis (RA), but the doses and regimens vary significantly. For this purpose, we conducted an observational study on the use of MTX for RA in Italy (MARI study).

Methods

The MARI study included 1,327 RA patients on MTX treatment for at least 12 months, at 60 Italian rheumatology units. Concomitant medications with corticosteroids, other DMARDs or biological therapies were recorded. The clinical assessment included the Disease Activity Score 28 (DAS28) and the serological positivity for the rheumatoid factor or for the anti-citrullinated protein antibodies.

Results

The included patients were treated with either oral (n=288) or parenteral (n=1039) MTX. Only 15.5% of the total number of the patients was on adequate MTX dose (i.e. ≥15 mg for the oral route of administration and >12 mg for the parenteral one). The initially established MTX dose was modified in 37.1% of the patients, for intolerance or clinical criteria. A DAS28 remission (DAS28 <2.6) was observed only in 58.5% of the cases, while 52.9% of the patients still presenting an active form of the disease were on suboptimal doses of MTX.

Conclusion

The weekly dose of MTX prescribed for the treatment of RA is often suboptimal, even in conditions of inadequate control of the disease activity. The recommendations for the use of MTX in RA patients should take into account the efficacy and tolerability data derived from its use in real clinical practice.

Key words

methotrexate, parenteral, oral, rheumatoid arthritis, therapy

Luca Idolazzi
Silvano Adami
Riccardo Capozza
Gerolamo Bianch
Annacarla Cozzolongo
Oscar Epis
Enrico Fusaro
Giovanni Lapadula
Alberto Migliore
Raffaele Pellerito
Angelo Pucino
Luigi Sinigaglia
Elisa Visalli
Maurizio Rossini

Please address correspondence to:
Luca Idolazzi,
Reumatologia,
Dipartimato di Medicina Interna,
Azienda Ospedaliera Universitaria Integrata,
Piazzale A. Stefani 1,
37126 Verona, Italy.
E-mail: luca.idolazzi@univr.it

Received on March 12, 2015; accepted in revised form on July 27, 2015.

Competing interests: none declared.

Introduction

Methotrexate (MTX) is the disease-modifying anti-rheumatic drug (DMARD) of first choice in the treatment of rheumatoid arthritis (RA), due to its efficacy, acceptable toxicity profile and low costs. It is also used to treat other inflammatory conditions, such as psoriasis, psoriatic arthritis, sarcoidosis and inflammatory bowel disease (1-3).

For patients who did not respond sufficiently, the MTX therapy can either be accompanied or replaced by a treatment with biologics or other non-biologic DMARDs.

The registration of MTX for the treatment of RA, and later for other rheumatic diseases, was based on a number of small studies, rather than adequately powered, randomised, placebo-controlled studies (RCTs), which have rigorous dosing, safety and efficacy objectives. Thus, despite broad experience in the field and the existence of official guidelines (4, 5), rheumatologists still prescribe MTX in a variety of ways *i.e.* at different doses and with different routes of administration, and interpret the safety profile in very different ways. Curtis *et al.* (6) have recently reported the prescribing habits of rheumatologists in their routine practice for RA patients in the United States; their study was based on administrative databases.

The aim of the MARI study was to monitor patients on MTX in 60 Italian rheumatology centers both cross-sectionally and longitudinally. We report the clinical data of these patients, with the aim of examining the prevalence of dosage, the preferred method of administration, the effectiveness of the treatment and the long-term safety profile.

Patients and methods

RA patients, fulfilling the 1987 classification criteria for RA of the American College of Rheumatology (7), and on treatment for at least 12 months with MTX, were included in an observational study at 60 rheumatology units across Italy. The centres were committed to recruit all consecutive patients meeting the inclusion criteria, over a period of 3–12 months (depending on the size of the centre) from the approval of the study protocol. The protocol was approved by the different Ethics Committees between December 2011 and October 2012. Recruitment was completed in October 2013.

The route of MTX administration was oral, subcutaneous or intramuscular. For the purpose of this report, subcutaneous and intramuscular forms of administration were pooled together and reported as 'parenteral MTX'. The following features of the disease were evaluated: duration of the symptoms, time elapsed since a definite diagnosis, time of first MTX treatment, changes in the MTX dose or route of administration after the first 12 months of therapy. The dose administered after the first 6 months since initiation of MTX therapy was considered the 'initial dose'. From previous studies (8-10). The absorption rate of MTX has been reported to decrease substantially for doses ≥15 mg/week (8), but we accepted this source of error for the limited number of patients taking such a high dose of MTX (see *Results*) for the oral form, the oral MTX dose was multiplied by a factor of 0.8, and here reported as 'oral adjusted dose'.

Concomitant medications were recorded, including: non-steroidal anti-inflammatory drugs, other DMARDs, such as leflunomide (LFN), hydroxyl-chloroquine (HCQ), sulfasalazine (SSZ), cyclosporine (CYC) and biological therapies (adalimumab, etanercept, infliximab, tocilizumab, golimumab, abatacept). The daily dose of corticosteroids, expressed as mg of prednisone (PN) equivalent, was categorised as <10 mg/day and ≥10 mg/day for the initial therapy, and as ≤5mg, 5–10 mg and >10 mg/day for the current therapy.

The clinical assessment included: both patient and rheumatologist's visual analogue scale (VAS) of the disease activity, the number of tender or swollen joints, the DAS28 score, the presence of a positive test for the rheumatoid factor (RF >40 U/ml) or for the anti-citrullinated protein antibodies (ACPA >20 U/ml). Patients were classified as having 'erosive arthritis', when an overt bone erosion was evident at the x-ray of the hand. The presence of typical extra-articular manifestations of the disease (skin, eyes, lung, kidney and heart) was also recorded. The study was approved by the lo-

cal Medical Ethics Committee and all patients gave signed Informed Consent.

Statistical analysis

Data are shown as either mean ± standard deviation (SD) or percentages. The distribution of variables was tested for normality. Differences between different groups of patients were evaluated using the ANOVA test for Analysis of Variance and followed by an independent *t*-test or, when appropriate, by a Mann–Whitney test or by a Pearson's χ^2-test for dichotomous variables. Probability (p) values <0.05 were considered statistically significant. All analyses were performed using a SPSS software v. 16.0 (Chicago, SPSS, Inc.).

Results

The initial cohort included 1,336 RA patients under treatment with MTX. Nine cases were excluded because their daily dose of MTX had not been recorded. The average age of the patients was 61.7±12.7; 80.2% were women. The main characteristics of the study population, according to the route of administration, are listed in Table I. The number of evaluable patients on oral MTX and parenteral MTX was 288 and 1039, respectively. Patients on oral MTX had a significantly longer duration of the disease than patients on parenteral MTX (13.2 *vs*. 11.6 years). The parenteral group presented higher VAS and DAS28 values, and a higher proportion of patients on high prednisone (PN) doses or bone erosion features.

MTX was more commonly prescribed in combination with HCQ in the oral group (p<0.01); while parenteral MTX was more frequently associated with other DMARDs (p<0.05). In one third of the patients in both groups, MTX prescription was associated with a biological therapy (mostly with etanercept, adalimumab and infliximab). The proportion of patients with positive RF or ACPA test was approximately equal in the two groups (63.8% for the oral group and 55.9% for the parenteral one).

MTX treatment began within 12 months of disease onset in 79% of the patients, with no observed difference between the two groups (Table II). Both initial and current mean MTX doses were higher in the parenteral group; this difference was more obvious when the oral dose was adjusted for a factor 0.8. By considering 'adequate' a weekly dose of MTX ≥15 mg for the oral route of administration and >12 mg for the parenteral route, the percentage of patients on adequate MTX doses was

Table I. Characteristics of RA patients on different route of administration of MTX. Values are reported as percentages or mean ± SD or median and 10–90% CI if not normally distributed (in brackets). ns: non-significant.

	Oral (n=288)	Parenteral (n=1039)	*p*-value
Female	80.5%	80.1%	ns
Postmenopausal	61.8%	61.5%	ns
Smoker	15.3%	14.8%	ns
Age	62.7 ± 13.4	61.0 ± 12.4	ns
Body weight	66.9 ± 13.7	68.7 ± 13.4	ns
Height	162.5 ± 8.1	163.5 ± 7.9	ns
Years since diagnosis	11 (1-25)	9 (1-14)	0.04
Initial oral daily dose of PN equivalent steroids			
None	22.6%	18.8%	ns
≤10 mg	65.3%	69.9%	
>10 mg	12.2%	10.9%	
Current oral daily dose of PN equivalent steroids			
None	55.9%	51.4%	0.003
≤5 mg	41.7%	41.7%	
>5 mg	2.4%	6.9%	
Other DMARDs			
HCQ	35.1%	26.7%	0.006
SSZ	3.8%	4.2%	
LFN	2.4%	3.9%	
CYC	2.4%	3.9%	0.05
Biological therapy	30.6%	32.7%	ns
AINS or analgesics	60.1%	58.4%	ns
Clinical assessment			
Patient VAS	6.0 ± 11.5	5.4 ± 11.5	0.003
Physician VAS	4.1 ± 8.4	4.4 ± 7.3	ns
DAS28	2.29 ± 0.96	2.51 ± 1.04	0.026
DAS28 <2.6	64.1%	56.6%	0.014
Bone erosion	52.4%	58.7%	0.034
Extra-articular manifestations	3.5%	5.4%	ns
Positive RF test	61.5%	64.4%	ns
ACPA-positive	51.4%	56.4%	ns

Table II. Characteristics of the MTX treatment in patients on oral or parenteral therapy.

	Oral	Parenteral	*p*-value
Beginning of MTX treatment			
At disease onset	15.6%	18.1%	ns
Within 3–6 months	12.2%	16.3%	
Within 7–12 months	53.5%	46.7%	
Within >12 months	18.1%	18.6%	
Folate supplements	96.5%	95.9%	ns
Mean initial weekly dose of MTX	10.8 ±3.2 [8.4 ±3.0]°	11.6 ±3.4	0.002 [0.000]°
Initial dose of MTX			
5 mg	1%	4.2%	
7.5 mg	12.1%	26.1%	
10–12.5 mg	49.4%	53.4%	0.000
15 mg	32.2%	13.6%	
≥20 mg	5.2%	2.7%	
Mean current weekly dose of MTX	10.4 ±3.1 [8.3 ±2.6]°	12.1 ±4.0	0.000
Current dose of MTX			
5 mg	5.6%	0.8%	
7.5 mg	29.2%	13.4%	
10 mg	39.2%	43.8%	0.000
10–12.5 mg	15.2%	23.6%	
12.5–15 mg	5.6%	10.2%	
≥15 mg	5.2%	8.2%	

°Dose corrected by a factor of 0.8.

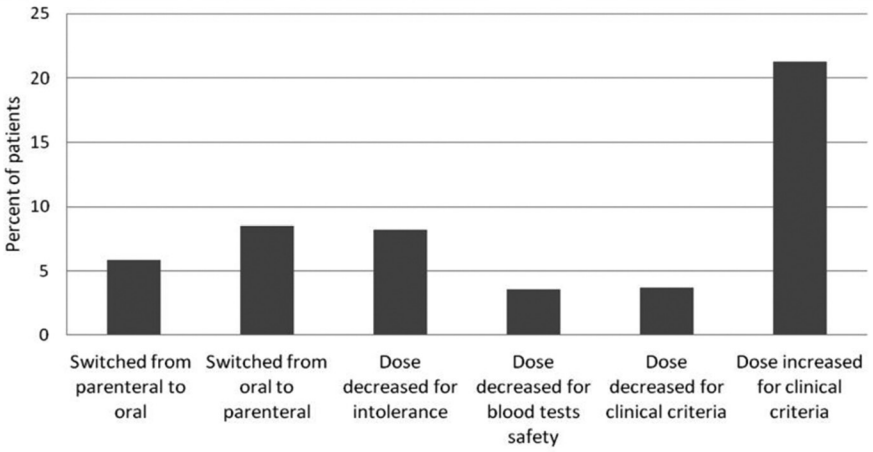

Fig. 1. Percentage of patients who have changed route of administration or dose of MTX.

Table III. Proportion of DAS28 values for different weekly doses of MTX.

MTX dose	DAS28 (ranks)				
	<2	2.01-2.59	3.50	>3.51	>2.6
≤5	54.2%	20.8%	8.3%	16.7%	25%
>5 – <10	47.5%	16.0%	18.2%	18.2%	36.4%
10 – <12.5	40.8%	17.1%	18.9%	23.3%	42.2%
12.5 – 15	36.0%	18.7%	17.3%	28.0%	45.3%
>15	39.7%	13.2%	26.5%	20.6%	47.1%
All	41.3%	17.1%	18.5%	23.0%	41.5%

as small as 5.2% in the oral group, and 18.4% in the parenteral group (an overall percentage of 15.5%).

A total of 78 patients (25%) initially on oral MTX began parenteral administration; while 113 (11%), initially on parenteral treatment began oral administration. The number of patients that had been on MTX for more than 12 months, but less than 18 months, was 278; this left 1049 patients for the analysis of dosage change after the initial phase. For 380 (37.1%) of this selected group of patients, the initially established dose of MTX was modified after at least 6 months from the first administration (Fig. 1). For 86 patients (8.3%) the dose was decreased because the patient found the treatment difficult to tolerate and for 37 patients (3.6%) the dose was decreased as a consequence of altered safety blood tests (anaemia or liver toxicity). Following clinical criteria, the dose was decreased in 19 patients (1.8%) and increased in 238 (22.7%). The mean increase was 0.43 ±3.73 mg/week for all subjects and 5.1±2.2 mg/week (median 5, IQ 3–5) for only those patients for whom the dose was increased (Fig. 1). The MTX dose was decreased in 39 patients on biological therapy and was instead increased, prior to initiation of the therapy, in 205 patients (data not shown). A DAS28 remission was observed in 58.5% of the patients.

Table III reports the DAS28 ranks for patients on different 'current' MTX doses, and the relative proportion. The MTX adjusted dose was positively related with DAS28 remission rates (p=0.013) (data not shown). Remarkably, 52.9% of the patients who were not on remission received suboptimal MTX doses (<15 mg/week); 20.6% of them were exclusively on MTX, while 4.5% were assuming MTX in association with another DMARD or biologics (data not shown).

For all these results no significant differences were observed across different centres or different structure (medical school or general hospital or out-patient clinics) or different regions.

Discussion

MTX is widely used for the treatment of RA, due to its efficacy, acceptable toxicity profile and low costs (1-3, 11). Systematic literature reviews recommend an initial therapeutic dose of 15 mg/week, which should be increased up to 25–30 mg/week (4, 5); it is recognised, though, that the average tolerable effective dose ranges between 15 and 20 mg/week. The preferred route of administration is generally oral, but as the bioavailability of parenteral MTX is higher with increasing doses (12, 13), a later change to parenteral administration is recommended, in the case of insufficient response to the drug (3, 14), as well as in the case of poor gastrointestinal tolerance (15, 16). These recommendations derive from the results of randomised controlled trials (RCTs) evaluating different dosages or routes of administration of MTX in RA, but the actual dose that rheumatologists prescribe in their real clinical practice is scarcely known.

In this study, 1,327 RA patients on MTX treatment for over one year, largely preferred the parenteral route of administration (78.3%) (Table I). Doses of MTX ≥20 mg/week were very uncommon, and the proportion of patients on doses close to what recommended by guidelines (3) was only 15.5%. The mean weekly dose of MTX was significantly higher in the case of the parenteral route, a difference even more striking when oral doses were adjusted for a factor of 0.8, assuming an intestinal absorption rate of 80% (Table II). A parenteral route and higher doses were prescribed to patients with more severe forms of the disease, as reflected by a significantly higher mean DAS28, a lower proportion of patients on DAS28 remission (<2.6), by more frequent erosive features and by the associated prescription of other DMARDs (*i.e.* SSZ, LFN and CYC) or a biologic.

In this study, the current dose of MTX was strongly influenced by the severity of the disease, precluding any conclusion on dose efficacy. On the other hand, our results suggest that, in common practice, rheumatologists tend to prescribe the lowest possible dose, even when the complete remission is not achieved. In this cohort, a DAS28 remission was observed in 58.5% of the patients, but 25.2% of them were on suboptimal parenteral MTX doses.

A large proportion of these patients (20.6% of the total) who was not on DAS28 remission and was under inadequate MTX treatment, was assuming exclusively MTX (no other DMARDs or a biologic).

Our results were compared with those obtained from large administrative databases of RA patients initiating MTX therapy in the US (6). The most obvious difference between our results and the US study is the route of administration, which in the US is parenteral only in less than 5% of the patients. The remarkable difference between the two countries (but more generally between Europe and the US) is likely explained by the cost of injectable MTX (very inexpensive in Italy) and by the propensity of Italian towards self-administration of parenteral formulations. The American study does not include a direct assessment of the disease activity, but it contains important information on the patients' adherence to treatment. This aspect will be addressed in the longitudinal part of this study. Here, we have collected information from most patients on the initially established MTX therapy and on the MTX therapy administered one year later. In 37.1% of the evaluable patients the MTX dose was adjusted within 12 months. In 12% of them, the dose was decreased, either for subjective or biochemical intolerance, indicating that, in a good proportion of patients, some degree of treatment intolerance may show-up well-beyond the first months of treatment. A step-up in the MTX dose was also very common (22.7% of the patients), with a median increase of 5 mg/week. As all these patients were not on DAS28 remission, our results suggest that the general preference of Italian rheumatologists is to increase the MTX dose very slowly. The introduction of the biologic was mainly preceded by an increase in the MTX dose. It is worth noting that, as this study evaluates the changes in the MTX dose occurring from the initial 'established' to the 'current' dose, we cannot exclude that the dose was considerably increased before the introduction of the biologic and later somewhat decreased. A DAS28 remission was observed in 58.5% of the patients on long-term MTX treatment for RA. Approximately, half of the patients who were not on remission were on suboptimal parenteral MTX dose (≤12.5 mg/week) and were not on concomitant treatment, with other DMARDs or a biologic. It appears, therefore, that, at variance with also the national guidelines (17, 18) for most rheumatologists the remission of the disease is not the primary therapeutic goal, but that patients' tolerance and the safety profile of the drug are more relevant (19).

Conclusions

The results of this study indicate that the weekly MTX dose for the treatment of RA is often suboptimal, despite inadequate control of the disease activity. Continuous adjustments of the dose are commonly required in routine clinical practice, even for patients who have been on treatment for a long time. The recommendations for the use of MTX in RA patients should take into account, not only data deriving from RCTs, but also efficacy and tolerability data derived from actual clinical practice and possible pitfalls in order to promote best practice in the treatment of RA

References

1. ALETAHA D, SMOLEN JS: The rheumatoid arthritis patient in the clinic: comparing more than 1,300 consecutive DMARD courses. *Rheumatology* (Oxford) 2002; 41: 1367-74.
2. MAETZEL A, WONG A, STRAND V, TUGWELL P, WELLS G, BOMBARDIER C: Meta-analysis of treatment termination rates among rheumatoid arthritis patients receiving disease-modifying anti-rheumatic drugs. *Rheumatology* (Oxford) 2000; 39: 975-81.
3. VISSER K, VAN DER HEIJDE D: Optimal dosage and route of administration of methotrexate in rheumatoid arthritis: a systematic review of the literature. *Ann Rheum Dis* 2009; 68: 1094-9.
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: 1086-93.
5. GOODMAN SM, CRONSTEIN BN, BYKERK VP: Outcomes related to methotrexate dose and route of administration in patients with rheumatoid arthritis: a systematic literature review. *Clin Exp Rheumatol* 2015; 33: 272-8.
6. CURTIS JR, ZHANG J, XIE F *et al*.: Use of oral and subcutaneous methotrexate in rheumatoid arthritis patients in the United States. *Arthritis Care Res* (Hoboken) 2014; 66: 1604-11.
7. ARNETT FC, EDWORTHY SM, BLOCH DA *et al*.: The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis Rheum* 1988; 31: 315-24.
8. SCHIFF MH, JAFFE JS, FREUNDLICH B: Head-to-head, randomised, crossover study of oral versus subcutaneous methotrexate in patients with rheumatoid arthritis: drug-exposure limitations of oral methotrexate at doses ≥15 mg may be overcome with subcutaneous administration. *Ann Rheum Dis* 2014; 73: 1549-51.
9. BAKKER MF, JACOBS JWG, WELSING PMJ *et al*.: Are switches from oral to subcutaneous methotrexate or addition of ciclosporin to methotrexate useful steps in a tight control treatment strategy for rheumatoid arthritis? A post hoc analysis of the CAMERA study. *Ann Rheum Dis* 2010; 69: 1849-52.
10. BRAUN J, KÄSTNER 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: 73-81.
11. YAZICI H: Methotrexate and not much harm to the lungs. *Clin Exp Rheumatol* 2014; 32 (6 Suppl. 87): S 10.
12. JUNDT JW, BROWNE BA, FIOCCO GP, STEELE AD, MOCK D: A comparison of low dose methotrexate bioavailability: oral solution, oral tablet, subcutaneous and intramuscular dosing. *J Rheumatol* 1993; 20: 1845-9.
13. HOEKSTRA M, HAAGSMA C, NEEF C, PROOST J, KNUIF A, VAN DE LAAR M: Bioavailability of higher dose methotrexate comparing oral and subcutaneous administration in patients with rheumatoid arthritis. *J Rheumatol* 2004; 31: 645-8.
14. PICHLMEIER U, HEUER K-U: Subcutaneous administration of methotrexate with a prefilled autoinjector pen results in a higher relative bioavailability compared with oral administration of methotrexate. *Clin Exp Rheumatol* 2014; 32: 563-71.
15. ROZIN A, SCHAPIRA D, BALBIR-GURMAN A *et al*.: Relapse of rheumatoid arthritis after substitution of oral for parenteral administration of methotrexate. *Ann Rheum Dis* 2002; 61: 756-7.
16. WEGRZYN J, ADELEINE P, MIOSSEC P: Better efficacy of methotrexate given by intramuscular injection than orally in patients with rheumatoid arthritis. *Ann Rheum Dis* 2004; 63: 1232-4.
17. DE LEONARDIS F, ALIVERNINI S, BONACCI E *et al*.: [Italian consensus on the recommendations about the use of methotrexate for the treatment of rheumatic diseases with a focus on rheumatoid arthritis: results from the «3E initiative»]. *Reumatismo* 2010; 62: 34-45.
18. TODOERTI M, MAGLIONE W, BERNERO E *et al*.: Systematic review of 2008-2012 literature and update of recommendations for the use of methotrexate in rheumatic diseases, with a focus on rheumatoid arthritis. 2013; 65: 207-18.
19. KRAUSE D, GABRIEL B, HERBORN G, BRAUN J, RAU R: The positive influence of methotrexate on the mortality of patients with rheumatoid arthritis is partly independent of its effect on disease activity: results of a re-evaluation 18 years after baseline. *Clin Exp Rheumatol* 2014; 32: 395-400.