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ORIGINAL ARTICLE

Response to methotrexate predicts long-term patient-related outcomes in rheumatoid arthritis

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Abstract This study was conducted to investigate the predictive value of the initial response to methotrexate (MTX) on long-term patient-related outcomes (PROs) in rheumatoid arthritis (RA). All RA patients starting MTX treatment between 1980 and 1987 in our department were enrolled in a prospective observational study. After an average of 18 years, patient-related outcomes were assessed in three dimensions according to the International Classification of Functioning, Disability and Health (ICF). Statistical analyses employed multivariable models with baseline values for age, gender, disease duration, rheumatoid factor positivity, disease activity, response to MTX after 1 year and continuous use of MTX as covariates. The 271 patients enrolled had a mean disease duration of 8.5 years, a mean number of swollen joints of 18 (out of 32), and a mean erythrocyte sedimentation rate of 55 mm/h. After 18 years, PRO was available in 89 patients (33 %). A clinical improvement of at least 20 % 1 year after the initiation of MTX was associated with a favourable outcome in all three dimensions of the ICF, independent of continuation of MTX ($p < 0.05$). The initial response to MTX is an independent predictor of PRO in RA as assessed after an average of 18 years.

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Introduction

Rheumatoid arthritis (RA) is a chronic disease characterized by inflammation of the peripheral joints potentially leading to joint deformities, impaired function, and disability. Patient-related outcome (PRO) measures have become increasingly important to assess the burden of rheumatic diseases and their impact on activities of daily living [1, 2]. Several clinical tools and biomarkers have been studied to examine their predictive value with regard to long-term PRO [3–5]. Thus, the degree of disease activity during the first year after diagnosis was found to predict 5-year outcomes of RA patients [6].

The conventional DMARD methotrexate (MTX) is a folic acid antagonist which is still used for the treatment of neoplastic disorders. It inhibits the synthesis of deoxyribonucleic acid, ribonucleic acid and proteins by binding to dihydrofolate reductase. Currently, MTX is also among the most commonly used drugs for the treatment of RA. A recent update of the previous Cochrane systematic review from 1997 evaluated the short-term benefits and harms of MTX for treating RA compared to placebo [7]. MTX plays a central role in current international recommendations for the management of RA [8, 9].

In order to establish whether an early response to MTX predicts long-term PRO even after 18 years, we analyzed the data of one of the oldest RA cohorts treated with MTX in Europe [10], established in Ratingen, Germany. At this point, MTX had not yet been approved for the treatment of RA despite early positive results [11, 12].

According to the three dimensions of outcome—"body functions and structure", "activities at the individual level"

and "participation in society"—which have been established by the International Classification of Functioning, Disability and Health (ICF) [13], we chose three endpoints for this post hoc analysis: the number of joints with deformities in the category "body functions and structure", self-reported physical functioning in the category "activities at the individual level" and self-sufficiency in the category "participation in society".

Patients and methods

Study population

Between January 1, 1980 and December 31, 1987, all patients with definite or classic RA [14] and a switch to MTX treatment were enrolled in this prospective observational study. Patients gave informed consent. The ethical standards of the Helsinki Declaration of 1975, as revised in 1983, were meticulously adhered to. All patients had previously been diagnosed with active disease and had shown insufficient response to at least one conventional DMARD other than MTX.

This prospective observational study was carried out with patients with mean disease duration of 8.5 years after pretreatment with other DMARDs such as gold and sulfasalazine [10]. One hundred forty-three patients continued the previous DMARD in full dosage (122 patients continued parenteral gold and 21 patients D-penicillamine or chloroquine) together with MTX. MTX was given intravenously or intramuscularly in dosages of 15–25 mg/week. Due to a lack of alternatives, MTX was even continued in case of a limited response. About 18 years after baseline, a re-evaluation was performed [15].

Clinical assessments

Clinical evaluations were performed at baseline and follow ups. Response to treatment was evaluated 1 year after baseline and rated as ≥20 % improvement or <20 % improvement. Improvement of ≥20 % was defined as a ≥20 % decrease in the swollen joint count (SJC) and in the erythrocyte sedimentation rate (ESR), with a prednisone dosage of <5 mg/day. A third group consisted of patients who had discontinued MTX treatment during the first year.

The re-evaluations of these patients were carried out in 1995 and 2003. They included the assessment of joint deformities (subluxation, luxation, contracture or ankyloses), especially Boutonnière deformities, swan-neck deformities, 90–90 thumb, ulnar drift of metacarpophalangeal joints, volar subluxation of the wrists, varus or valgus deformities of the knees and forefeet deformities. A total of 38 joints were assessed: proximal interphalangeal and metacarpophalangeal joints, wrists, elbows, shoulders, knees, ankles and metatarsophalangeal joints II–V.

Self-reported physical functioning was measured by a German questionnaire (Funktionsfragebogen Hannover) the result of which closely correlates with the health assessment questionnaire (HAQ) [16]. Patients were interviewed about their individual degrees of self-sufficiency (0 = self-sufficient, 1 = dependent on others for help).

Statistical analysis

The analysis was planned for three hierarchical steps: The first step was a multivariate regression analysis for the association of the response to MTX treatment after 1 year (≥20 % improvement or <20 % improvement) and the number of joints with deformities (out of 38) after 18 years. The following covariates were chosen: baseline values of age, gender, disease duration, rheumatoid factor (RF) positivity, swollen joint count (SJC), erythrocyte sedimentation rate (ESR) and patient global assessment as well as continuation of MTX treatment until 1995. In case of significant association ($p < 0.05$), the second step included a multivariate regression analysis for the association of the response to MTX treatment after 1 year and self-reported physical functioning 18 years after baseline, using the same covariates. If these associations were significant, the last analysis would be logistic regression for the association of response to MTX treatment and self-sufficiency, once again employing the above mentioned covariates.

SAS, version 9.3 (SAS Institute, Cary, NC) was used for statistical analysis

Results

Patient characteristics at baseline

Two hundred seventy-one RA patients were included in the study between 1980 and 1987 with a mean age of 58 years and mean disease duration of 8.5 years. About 95 % of the patients had joint erosions. The disease activity at baseline was high (mean number of swollen joints; 18 (out of 32), mean ESR; 55 mm/h). About 96 % of the patients took NSAIDs and 62 % prednisone (mean dosage of 4.5 mg/day). Nearly, all of these patients rated their global disease activity as severe [10].

Treatment and response after 1 year

One year after baseline, 179 patients showed ≥20 % improvement (66 %); 55 patients had <20 % improvement but continued MTX treatment (20 %) and 37 patients had discontinued MTX treatment due to side effects, mostly nausea, vomiting or stomatitis (14 %).

Patient evaluation 18 years after baseline

Since baseline, 147 patients (54 %) had died due to cardiovascular disease ($n=53$, 36.1 % of all deceased patients), cancer ($n=16$, 10.9 %), gastrointestinal diseases ($n=10$, 4 %), pneumonia ($n=7$, 2.8 %), renal failure ($n=4$, 1.6 %), cachexia ($n=9$, 3.6 %), suicide ($n=1$), septicemia or infection ($n=3$, 1.2 %) or atlantodental dislocation ($n=1$) (in 43 patients [29.3 %] the cause of death could not be determined) [15]. Fourteen patients (5 %) could only be interviewed by telephone, and 21 patients (8 %) were not available for follow-up. Thus, patient-related outcome could be assessed in 89 out of 271 patients (33 %).

Using multiple regression analysis, significant predictors of the number of joints with deformities 18 years after baseline were disease duration ($p<0.0001$) and response to MTX treatment after 1 year ($p=0.0205$) (Table 1).

Self-reported physical functioning (available for 85 of these 89 patients) was significantly associated with age ($p=0.0018$), disease duration ($p=0.0117$) and response to MTX treatment 1 year after baseline ($p=0.0004$) (Table 2). The third dimension (represented by self-sufficiency) was again associated with age ($p=0.0068$), disease duration ($p=0.0117$) and response to MTX treatment 1 year after baseline ($p=0.0199$) (Table 3).

Discussion

In this post hoc multivariate analysis of a historical prospective observational single centre study of active RA patients treated with MTX in a dosage of 15–25 mg/week after 8.5 years of disease duration, we found mainly two parameters that predict long-term PRO: disease duration and response to MTX. All patients had very active and severe disease as shown by the swollen joint count, the ESR and the radiographic damage already present in many patients.

MTX therapy yielded an improvement of at least 20 % in 66 % of patients after 1 year. This initial response was predictive for PRO 18 years after baseline—irrespective of the continuation of MTX treatment in these years. This effect remained significant after adjusting for age, gender, disease duration, signs of baseline disease activity such as swollen joint count and ESR and baseline patient global assessment.

These findings are supported by a recent study which shows that the chance of being in remission after 5 years is more than twice as high for patients in remission (DAS28 < 2.6) after 6 and 12 month compared to those in a state of moderate disease activity (DAS 28 3.2–5.1) at these times; there are also significant differences regarding the functional capacity as measured by the Health Assessment Questionnaire-Disability Index (HAQ-DI) and the number of missed workdays which was fivefold in comparison with the group of patients who had no sustained remission during the first year [6].

In the FIN-RACo trial, good response after 6 months of treatment was associated with smaller numbers of days with sick leave from 6 months through 60 months. ACR50 response at 6 months had not been proved more beneficial than ACR20 response with regard to work disability, while patients without ACR20 response had a high risk for work disability [17].

Baseline radiologic damage was not included in our model because radiologic data were not available for all patients. Nonetheless, we had shown for the subgroup of our cohort with available radiologic date that baseline radiologic damage may be a good long-term predictor of PRO [18], as had been pointed out by data from a French cohort [19]. In this subgroup, response to MTX treatment was an independently significant predictor in only two of the three ICF dimensions [18]. Therefore, we performed this post hoc analysis to include all patients.

Unfortunately, there were no baseline data concerning the smoking habits or the socioeconomic status of our patients. Thus, these prognostic factors could not be included in the analysis. Bias may occur by the fact that 54 % of the patients

Table 1 Predictors of the number of joints with deformities 18 years after baseline

Variable	Parameter estimate	Standard error	*p* value
Age at baseline	0.1175	0.1245	0.3481
Female gender	0.8272	2.9201	0.7777
Disease duration	0.8752	0.1870	*<0.0001*
Rheumatoid factor positivity at baseline	0.5993	2.9708	0.8406
Swollen joint count at baseline	0.2086	0.1425	0.1472
ESR at baseline	0.0757	0.0403	0.0638
Patient global assessment at baseline	−1.7384	2.2614	0.4444
<20 % improvement 1 year after baseline	2.3950	1.0132	*0.0205*
MTX treatment 10 years after baseline	0.1650	0.1642	0.3181

ESR erythrocyte sedimentation rate, *MTX* methotrexate

Numbers in italics are significant at $p<0.05$

Table 2 Predictors of self-reported physical functioning (German questionnaire: Funktionsfragebogen Hannover) 18 years after baseline

Variable	Parameter estimate	Standard error	*p* value
Age at baseline	−1.1235	0.3471	*0.0018*
Female gender	−9.2336	7.6564	0.2316
Disease duration	−1.2800	0.4951	*0.0117*
Rheumatoid factor positivity at baseline	−1.8129	7.7984	0.8168
Swollen joint count at baseline	−0.3770	0.3751	0.3182
ESR at baseline	−0.1028	0.1092	0.3497
Patient global assessment at baseline	−0.0903	5.9169	0.9879
<20 % improvement 1 year after baseline	−9.9113	2.6718	*0.0004*
MTX treatment 10 years after baseline	−0.8165	0.4493	0.0732

ESR erythrocyte sedimentation rate, *MTX* methotrexate

Numbers in italics are significant at $p < 0.05$

died in the 18 years of follow up. Although, mortality in this population is associated to non-response to MTX [15]. Therefore, this fact makes a bias less likely.

It needs to be stressed that the reported observations cannot be explained by the "window of opportunity" paradigm [20], since, which distinguishes this study from the French ESPOIR cohort [6], the patients in our historical cohort already had a mean disease duration of 8.5 years when MTX treatment was first started.

Thus, good initial response to MTX treatment seems to be a long-term predictor of PRO, irrespective of the actual use of MTX, in severely affected RA patients with an already relatively long disease duration. The factors determining MTX response in RA patients are only partly understood. As shown in the SWEFOT study, there are clinical predictors of worse short-term response to MTX treatment such as current smoking, female sex, longer symptom duration and younger age [21].

Besides, pharmacogenetic and pharmacogenomic features may trigger response to methotrexate treatment in RA [22, 23]. Numerous gene polymorphisms with possible effects on MTX efficacy are described in the MTX transporter and glutamination genes, the ATP-binding cassette (ABC) family genes, the folate pathway genes, the thymidylate synthase genes and the adenosine pathway genes [24–28].

Thus, the degree of response to MTX may be determinated not only by clinical features such as current smoking or longer disease duration but also by different genetic backgrounds, thus leading to different long term PRO. Since we could not perform such analyses in our cohort at this point in time, we cannot confirm the role of these genetic influences in our study. However, even though the knowledge on this subject seems to rise continuously, there is still no role for such tests in the management of RA. Nevertheless, this may change in the future.

It remains unclear whether the observed relatively favourable outcomes for those patients with sustained remission in the first year are due to low disease activity and the lower burden of inflammation or whether the response to MTX during the first year partly mirrors an independent feature of the individual patient and his genome. Unfortunately, our data do not allow to pursue this question that may be left to future scientific work.

Our data confirm the effectiveness of MTX in longstanding disease and add the predictive value of a positive response for long-term outcomes.

Table 3 Predictors of self-sufficiency 18 years after baseline (logistic regression)

Variable	Odds ratio	95 % confidence interval	*p* value
Age at baseline	0.900	0.834–0.971	*0.0068*
Female gender	0.685	0.140–3.349	0.6405
Disease duration at baseline	0.870	0.781–0.970	*0.0117*
Rheumatoid factor positivity	0.412	0.078–0.2.159	0.2938
Swollen joint count at baseline	1.003	0.933–1.078	0.9450
ESR at baseline	0.999	0.978–1.022	0.9590
Patient global assessment at baseline	0.456	0.126–1.652	0.2319
<20 % improvement 1 year after baseline	0.504	0.283–0.897	*0.0199*
MTX treatment 10 years after baseline	0.947	0.870–1.031	0.2079

ESR erythrocyte sedimentation rate, *MTX* methotrexate

Numbers in italics are significant at $p < 0.05$

Compliance with ethical standards

Disclosures None.

References

1. El Miedany Y (2013) PROMs in inflammatory arthritis: moving from static to dynamic. Clin Rheumatol 32:735–742
2. Kingsley G, Scott IC, Scott DL (2011) Quality of life and the outcome of established rheumatoid arthritis. Best Pract Res Clin Rheumatol 25:585–606
3. Malm K, Bergman S, Andersson M, Bremander A, BARFOT study group (2015) Predictors of severe self-reported disability in RA in a long-term follow-up study. Disabil Rehabil 37:686–691
4. Tanaka E, Mannalithara A, Inoue E, Hara M, Tomatsu T, Kamatani N, Singh G, Jamanaka H (2008) Efficient management of rheumatoid arthritis significantly reduces long-term functional disability. Ann Rheum Dis 67:1153–1158
5. Balsa A, Del Amo J, Blanco F et al (2010) Prediction of functional impairment and remission in rheumatoid arthritis patients by biochemical variables and genetic polymorphisms. Rheumatology (Oxford) 49:458–466
6. Combe B, Logeart I, Belkacemi MC, Dadoun S, Schaeverbeke T, Daurès JP, Dougados M (2015) Comparison of the long-term outcome for patients with rheumatoid arthritis with persistent moderate disease activity or disease remission during the first year after diagnosis: data from the ESPOIR cohort. Ann Rheum Dis 74:724–729
7. Lopez-Olivo MA, Siddhanamatha HR, Shea B, Tugwell P, Wells GA, Suarez-Almazor ME (2014) Methotrexate for treating rheumatoid arthritis. Cochrane Database Syst Rev 6:CD000957. doi:10.1002/14651858.CD000957.pub2
8. Singh JA, Furst DE, Bharat A et al (2012) 2012 update of the 2008 American college of rheumatology recommendations for the use of disease-modifying antirheumatic drugs and biologic agents in the treatment of rheumatoid arthritis. Arthritis Care Res 64:625–639
9. Smolen JS, Landewé R, Breedveld FC et al (2010) EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs. Ann Rheum Dis 69:964–975
10. Krause D, Schleusser B, Herborn W, Rau R (2000) Response to methotrexate is associates with reduced mortality in patients with severe rheumatoid arthritis. Arthritis Rheum 43:14–21
11. Wilke WS, Calabrese LH, Scherbel AL (1980) Methotrexate in the treatment of rheumatoid arthritis; pilot study. Cleve Clin Q 47:305–309
12. Weinblatt ME, Coblyn JS, Fox DA, Fraser PA, Holdsworth DE, Glass DN, Trendham DE (1985) Efficacy of low-dose methotrexate in rheumatoid arthritis. N Engl J Med 312:818–822
13. World Health Organization Assessment, Classification and Epidemiology Group (1999) International Classification of Functioning, Disability and Health. World Health Organization, Geneva
14. Ropes MW, Bennett GA, Cobb S, Jacox RF, Jessar RA (1995) 1958 revision of diagnostic criteria for rheumatoid arthritis. Bull Rheum Dis 9:175–176
15. Krause D, Gabriel B, Herborn G, Braun J, Rau R (2014) 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 32:395–400
16. Zochling J, Stucki G, Grill E, Braun J (2007) A comparative study of patient-reported functional outcomes in acute rheumatoid arthritis. J Rheumatol 34:64–69
17. Puolakka K, Kautiainen H, Möttönen T, FIN-RACo Trial Group et al (2005) Early suppression of disease activity is essential for maintenance of work capacity in patients with recent-onset rheumatoid arthritis: five-year experience from the FIN-RACo trial. Arthritis Rheum 52:36–41
18. Krause D, Gabriel B, Herborn G, Braun J, Rau R (2015) Radiologic damage at baseline predicts patient related outcomes 18 years after the initiation of methotrexate therapy in patients with severe rheumatoid arthritis. Clin Exp Rheumatol 33:611–616
19. Combe B, Cantagrel A, Goupille P et al (2003) Predictive factors of 5-year health assessment questionnaire disability in early rheumatoid arthritis. J Rheumatol 30:2344–2349
20. van Nies JA, Krabben A, Schoones JW, Huizinga TW, Kloppenburg M, van der Helm-van Mil AH (2014) What is the evidence for the presence of a therapeutic window of opportunity in rheumatoid arthritis? A systematic literature review. Ann Rheum Dis 73:861–870
21. Saevarsdottir S, Wallin H, Seddighzadeh M, Ernestam S, Geborek P, Petersson IF, Bratt J, van Vollenhoven RF, SWEFOT Trial Investigators Group (2011) Predictors of response to methotrexate in early DMARD naive rheumatoid arthritis: results from the initial open-label phase of the SWEFOT trial. Ann Rheum Dis 70:469–475
22. Zhu H, Deng FY, Mo XB, Qiu YH, Lei SF (2014) Pharmacogenetics and pharmacogenomics for rheumatoid arthritis responsiveness to methotrexate treatment: the 2013 update. Pharmacogenomics 15:551–566
23. Fransen J, Kooloos WM, Wessels JA, Huizinga TW, Guchelaar HJ, van Riel PL, Barrera P (2012) Clinical pharmacogenetic model to predict response of MTX monotherapy in patients with established rheumatoid arthritis after DMARD failure. Pharmacogenomics 13:1087–1094
24. Brinker RR, Ranganathan P (2010) Methotrexate pharmacogenetics in rheumatoid arthritis. Clin Exp Rheumatol 28(Suppl 61):33–39
25. Wessels JA, de Vries-Bouwstra JK, Heijmans BT et al (2006) Efficacy und toxicity of methotrexate in early rheumatoid arthritis are associated with single-nucleotide polymorphisms in genes coding for folate pathway enzymes. Arthritis Rheum 54:1087–1095
26. Kato T, Hamada A, Mori S, Saito H (2012) Genetic polymorphisms in metabolic and cellular transport pathway of methotrexate impact clinical outcome of methotrexate monotherapy in Japanese patients with rheumatoid arthritis. Drug Metab Pharmacokinet 27:192–199
27. Dervieux T, Furst D, Lein DO, Capps R, Smith K, Walsh M, Kremer J (2004) Polyglutamation of methotrexate with common polymorphisms in reduced folate carrier, aminoimidazole carboxamide ribonucleotide transformylase, and thymidylate synthase are associated with methotrexate effects in rheumatoid arthritis. Arthritis Rheum 50:2766–2774
28. Ponchel F, Goëb V, Parmar R et al (2014) An immunological biomarker to predict MTX response in early RA. Ann Rheum Dis 73:2047–2053