Predictors of Clinical Response and Radiographic Progression in Patients with Rheumatoid Arthritis Treated with Methotrexate Monotherapy

JULIE DROUIN and BOULOS HARAOUI, for The 3e Initiative Group

ABSTRACT. ***Objective.*** To determine through a systematic literature search the predictors of clinical response and radiographic progression in adult patients with rheumatoid arthritis (RA) treated with methotrexate (MTX) monotherapy.

Methods. A systematic literature search using Medline, Embase, and the Cochrane Central Register of Controlled Trials, in May 2008, and review of abstracts of the annual congresses of the American College of Rheumatology (2006–2007) and the European League Against Rheumatism (2002–2007) was performed, as part of a national initiative to develop guidelines for the use of MTX in RA.

Results. Nine studies fulfilled the criteria set for this literature search. Male sex, low disease activity measured by composite scores (DAS or SDAI), and nonutilization of prior DMARD were predictive of good clinical response to MTX. Patients with early RA who are rheumatoid factor-positive and smokers tend to have lower response. However, this last association has not been found for patients with established disease. High disease activity before introduction of MTX monotherapy and higher activity during followup at 3 months is a predictor of more severe radiographic progression.

Conclusion. Among factors found to be predictive of clinical and radiographic outcomes of patients with RA treated with MTX, no factor was found to have a high predictive value. Variability in efficacy measures and statistical tests made it difficult to compare results. Followup of disease activity after 3 to 6 months of treatment seems to be a better and more useful predictor than baseline patient characteristics. (First Release May 1 2010; J Rheumatol 2010;37:1405–10; doi:10.3899/jrheum. 090838)

Key Indexing Terms:
RHEUMATOID ARTHRITIS METHOTREXATE SYSTEMATIC REVIEW PROGNOSIS

The therapeutic arsenal for treating rheumatoid arthritis (RA) has greatly diversified over the last decade. From the perspective of offering patients optimal treatment, i.e., clinical and radiological remission of disease at the lowest cost while avoiding adverse effects, it would be important to predict which patients will respond to a particular treatment. Methotrexate (MTX), used alone or in combination with other disease-modifying antirheumatic drugs (DMARD) or with a biologic agent, is the cornerstone of RA therapy.

We conducted a systematic literature review as part of the 3e Initiative (evidence, expertise, exchange) in Rheumatology, a national initiative aimed at developing recommendations for the use of MTX in RA. Our research question was: In adult patients with RA, what are the predictors of clinical response to MTX monotherapy and which factors predict radiological nonprogression? We specifically examined characteristics of patients and of their disease as prognostic factors. Study of the pharmacogenetic factors associated with MTX efficacy will be carried out at a later time.

MATERIALS AND METHODS

We searched for articles in French and English, using the Medline (1950–2007), Embase (1980–2007), and Cochrane Central Register of Controlled Trials (1999–2007) search engines in October 2007. We used the keywords "rheumatoid arthritis," "methotrexate," "randomized controlled trial, clinical trial, comparative study, followup studies, meta-analysis," "treatment outcome," "effica$, effecti$, predict$, respon$, prognos$" and their derivatives.

We also manually searched for relevant articles in the references in the selected articles and the European League Against Rheumatism (EULAR) 2002–2007 and American College of Rheumatology (ACR) 2006–2007 meeting abstracts. To be included, articles had to contain data collected from randomized studies, metaanalyses, or prospective studies involving adult patients with RA (age > 18 yrs) treated with MTX alone. We excluded articles with the following characteristics: pediatric population, non-RA, poorly defined response criteria, insufficient number of patients, review articles, guidelines papers, case reports, commentary, letters, or languages other than French or English. We also excluded articles where the patients had received various DMARD therapies and where there was no analysis

From the Division of Rheumatology, Department of Medicine, Centre Hospitalier de l'Université de Montréal, Université de Montréal, Montréal, Québec, Canada.

Supported by an unrestricted grant from Abbott Laboratories

J. Drouin, MD, Rheumatology Fellow; B. Haraoui, MD, Clinical Associate Professor.

Address correspondence to Dr. B. Haraoui, CHUM, Campus Notre-Dame, Département de rhumatologie, 1560 Sherbrooke est, Montreal, Quebec H2L 1S6, Canada. E-mail: bharaoui@videotron.ca

Accepted for publication November 20, 2009.

from which we could determine the predictive factors for the MTX-only group.

Using Hayden's recommendations[1], we analyzed the quality of each article selected in order to determine the risk of major biases that could disqualify it. We ranked the risk of bias as weak, moderate, or high.

Given the wide heterogeneity of the articles, the different definitions of "clinical response" used, and their different analytical methods, which did not consider the same confounding factors, we were unable to statistically pool the data to perform a metaanalysis. We simply extracted data from each article and pooled them in a table in a way to give a global idea of the actual literature conclusions on our question.

We separated the data to check if the predictors of response to MTX differ between early arthritis and established arthritis.

RESULTS

The search performed on October 23, 2007, yielded 2030 articles from Medline, 3312 from Embase, and 392 from Cochrane Central Register of Controlled Trials. Most were excluded by reading the title and abstract, 237 were reviewed, and 5 met our inclusion and quality criteria[2-6]. We also included 3 ACR and EULAR abstracts[7-9]. A search update performed in May 2008 yielded an additional article[10].

The selected studies are described in Table 1.

Predictive factors of clinical response to MTX. Table 2 presents patient characteristics and their association with response to MTX. Age and renal function do not seem to affect response to MTX. A metaanalysis[2], whose primary objective was to examine the influence of these 2 factors, did not find a correlation with the response to treatment. In all the studies, female sex was a poor prognostic factor for response to MTX. In a study by Wessels, *et al*[3], which involved patients with early RA (subgroup of the BeST study), premenopausal women responded poorly to MTX.

Surprisingly, the presence of a positive rheumatoid factor (RF) or a positive anti-cyclic citrullinated peptide (CCP; investigated in only one study[3]) was not a good predictive response marker, especially in patients with established disease. However, in Wessels' study of early RA[3], the RF-positive patients tended (nonstatistically significant) to respond less well to treatment. If they were smokers and seropositive, they clearly did not respond to MTX as well (OR 0.1).

Patients who had previously tried other DMARD therapies responded less well to MTX, irrespective of duration of their disease. Studies by Wessels, *et al*[3] and Hoekstra, *et al*[4] did not show a link between duration of disease and response to MTX. Nor was such a link found in a study by Lie, *et al*[7], where there was a statistically nonsignificant trend ($p = 0.07$). However, it should be noted that the duration of disease in the study by Wessels, *et al*[3] was limited to 2 years.

Table 3 shows the different measures of disease activity assessed at the start of treatment and their influence on the response to MTX. In all the studies, the degree of disease activity measured by the Disease Activity Score (DAS) and

Table 1A. Selected studies for predictors of clinical response to MTX.

Study Design	Reference	No. Patients, No. Studies	Treatment/Followup	Outcome Measured	Risk of Bias/ Oxford Level
Metaanalysis	Felson[2], RA Clinical Trial Archive Group	496 11 RCT	MTX alone (different clinical trials) only predictors studied: age and renal function	Major clinical improvement: 50% of TJC, SJC	Moderate/2a
	Aletaha[10]	462 3 RCT	MTX alone (different clinical trials)	Correlation with SDAI at 1 yr	Moderate/2a
Prospective studies in early RA	Wessels[3], BeSt	205	MTX up to 25 mg; followup: 6 mo	Good clinical response, DAS < 2.4	Low/2b
Prospective studies in established RA	Hoekstra[4]	411	MTX up to 25 mg +/– folate; followup: 48 wks	EULAR response, DAS < 2.4 and diminution > 1.2	Low/2b
	Lie[7], Norwegian Registry	876	MTX (dose not mentioned); followup: 6 mo	EULAR good response, DAS28 < 3.2 and diminution > 1.2	Moderate/2b

Table 1B. Selected studies for predictors of radiological damage progression to MTX.

Study Design	Reference	No. Patients	Treatment	Radiologic Score	Risk of Bias/ Oxford Level
Prospective RCT in early active RA (except for TEMPO)	Smolen[5], ASPIRE	1004 total 298 MTX	MTX 20 mg; followup: 54 wks	Modified Sharp/Van der Heijde	Low/2b
	Weinblatt[8], TEMPO and ERA	212 TEMPO (71 early RA subgroup) 213 ERA	MTX 20 mg; followup: 52 weeks	Total Sharp score	Moderate/2b
	Rau[6]	87	MTX 15 mg; followup: 1 yr	Modified Larsen and Sharp	Low/2b
	Van der Heijde[9], PREMIER	187	MTX 20 mg; followup: 1 yr	Total Sharp score	Moderate-high/4 (lack of information)

Table 2. Predictors of clinical response to MTX: patients and disease characteristics.

Factors	Predictor of Response?	Multivariate Analysis OR	Univariate Analysis	Studies	Type of Study
Age	No	NS	NS	All studies	All
Renal function	No	NS		Felson[2]	Metaanalysis
		NS	NS	Wessels[3]	Early RA
		OR 0.99	OR 0.99	Hoekstra[4]	Established RA
Ethnicity	No data				
Sex	Yes; men respond better vs women	OR 0.3 premenopausal OR 0.5 postmenopausal trend	Yes	Wessels[3]	Early RA
		OR 1.75 (men) OR 0.69 (women)	OR 1.79	Hoekstra[4], Lie[7]	Established RA
RF + combined with smoking	Yes; respond less	OR 0.1	NS	Wessels[3]	Early RA
RF+	Trend in early RA;	OR 0.5 (0.2–1.2), trend	Trend	Wessels[3],	Recent-onset RA
	no in established RA	NS	NS	Hoekstra[4], Lie[7]	Established RA
Anti-CCP +	No (1 study only)	NS	NS	Wessels[3]	Early RA
Smoking	No	NS	Trend	Wessels[3]	Early RA
Prior DMARD	Respond less	OR 0.81		Lie[7]	Established RA
Disease duration	Uncertain	NS	NS	Wessels[3]	Early RA
		NS OR 0.88 (5 yr duration), trend p = 0.07		Hoekstra[4], Lie[7]	Established RA

NS: not statistically significant; DMARD: disease modifying antirheumatic drugs; CCP: cyclic citrullinated peptide.

Table 3. Predictors of clinical response to MTX: disease activity at baseline. When no number is given, a dichotomous yes/no indicates if the factor is a significant predictor.

Factors	Predictor of Response? Yes/No	Multivariate Analysis	Univariate Analysis	Reference	Type of Study
High DAS at baseline	Yes, less response if DAS high	OR 0.1 (DAS > 3.8)	Yes	Wessels[3]	Early RA
		OR 0.53	OR 0.52	Hoekstra[4]	Established RA
SDAI	Yes. Low but significant correlation			Aletaha[10]	Early RA
At baseline	between SDAI at baseline and at 1 yr.		r = 0.256		
1 mo	Correlation higher for SDAI at 3 mo		r = 0.436		
2 mo			r = 0.533		
3 mo			r = 0.593		
6 mo			r = 0.682		
ESR	Uncertain	No	Yes	Wessels[3]	Early RA
		OR, 0.91 (for 10 mm)	—	Lie[7]	Established RA
CRP	No	No	Trend	Wessels[3]	Early RA
		No	No	Lie[7]	Established RA
SJC	Yes in early RA	Yes	Yes	Wessels[3]	Early RA
	No in established RA	No	—	Lie[7]	Established RA
TJC, feet = 4	Yes for feet (not TJC)	Yes, OR 0.55		Lie[7]	Established
HAQ	Yes in early RA	Yes	Yes	Wessels[3]	Early RA
	No in established RA	No	—	Lie[7]	Established RA
Patient global assessment	No	No	Yes	Wessels[3]	Early RA
		No		Lie[7]	Established RA
Physician global assessment	No	No	Yes	Wessels[4]	Early RA
		No	—	Lie[7]	Established RA
Pain VAS	No	No	Yes	Wessels[3]	Early RA
		—	No	Lie[7]	Established RA
Erosion score	No	—	No	Lie[7]	Established RA

r: correlation coefficient; DAS: Disease Activity Index; SDAI: Simplified Disease Activity Index; SLC: swollen joint count; TJC: tender joint count; VAS: visual analog scale.

the Simplified Disease Activity Index (SDAI) predicted a poorer response to MTX. Aletaha, *et al*[10] measured the coefficient of correlation between the degree of disease activity measured at baseline (by the SDAI, DAS28, and Clinical

Disease Activity Index, CDAI) and after one year of treatment. The correlation was significant, but low (r = 0.256). It increased when disease activity was measured during treatment and became more predictive after 3 months of treatment (r = 0.593). Inflammatory variables [C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR)], as well as swollen joint count, tender joint count, and patient and physician global assessment, when considered separately, were poor predictors. Some of these variables had a strong correlation with the DAS and are therefore not independent factors in the multivariate models. CRP did not emerge as a predictor. ESR correlated with the clinical response in some studies but did not seem to be an independent factor in the study of early RA by Wessels, *et al*[3]. In that study, a high swollen joint count and a high Health Assessment Questionnaire score emerged as predictive factors of nonresponse to MTX. They were not prognostic factors in the study by Lie, *et al*[7] involving a population of patients with arthritis of longer duration; and presence of radiographic joint erosions did not correlate with clinical response to treatment.

Predictive factors of radiological progression in patients taking MTX. Table 4 shows the factors that predict radiological progression. Most studies involved a population of patients with early arthritis, except a subgroup of 141 patients in the TEMPO trial[8] where patients had an average disease duration of 6.8 years. The analysis of the ASPIRE trial[5] included the largest number of patients and examined the influence of several significant factors (except anti-CCP).

Age and sex did not influence radiological progression. A positive RF had the greatest correlation with radiological progression, but seropositivity was not an independent predictive factor, as shown by the multivariate models in which the disease activity variables were included[5,6].

High disease activity is the factor that correlates best with radiological progression. High inflammatory variables at baseline, such as the ESR and CRP, are strongly associated with radiological deterioration. The ESR seems to be a better predictive factor than CRP, which was not significant in the multivariate models that included ESR. There was a correlation between the swollen joint count and radiological progression, but not for tender joint count. Further, the persistence of disease activity measured during treatment correlates with radiological progression, according to certain univariate models[5,8].

The study by Smolen, *et al*[5] did not show a correlation between the radiological score at the start of treatment and radiological progression with MTX. This is the only article that examined this factor.

DISCUSSION

In our literature review, we identified factors that influence response to MTX used as monotherapy. Male sex, low disease activity measured by the DAS or SDAI, and not having previously used DMARD are the strongest determining factors of a good clinical response to MTX. The presence of a positive RF in combination with smoking is predictive of a lesser response in patients with early arthritis. This relationship was not found for patients with established arthritis. In addition, the presence of anti-CCP was not a predictive factor; however, it was explored in only one study. The percentage of anti-CCP-positive patients in this study was 44% and 52% in the responder and nonresponder groups, respectively, which is possibly a little lower than expected.

Table 4. Predictors of radiographic progression with MTX treatment.

Factors	Multivariate Analysis	Univariate Analysis	Reference
Age	No	No	Smolen[7]
Sex	No	—	Smolen[7]
Ethnicity	No data		No Data
RF+	No	Yes, r = 0.127	Smolen[7]
	No	Yes	Rau[9]
Anti-CCP	No data for MTX alone		
Baseline radiographic score	No	No	Smolen[7]
High ESR, per unit	Yes, OR 1.02	Yes, r = 0.268	Smolen7
	Yes, B = 0.49	Yes, r = 0.41	Rau[9]
High CRP, per unit	No*	Yes, r = 0.242	Smolen[7]
	No	No	Rau[9]
	Yes, OR 1.139**	Yes	Van der Heijde[10]
High TJC	No	No	Smolen[7]
	No	No	Rau[9]
High SJC (per swollen joint)	Yes, OR 1.04	Yes, r = 0.156	Smolen[7]
	No	No	Rau[9]

* CRP is significant in multivariate model that exclude the ESR; ** ESR was not in the multivariate model tender joint count. r: correlation coefficient; B: beta coefficient; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; SJC: swollen joint count; TJC: tender joint count.

It should be noted that no factor had a sufficient correlation for predicting with certainty a response or nonresponse to MTX. Wessels, *et al*[3] attempted to construct a clinical and pharmacogenetic model that would predict the efficacy of MTX in patients with early RA. The clinical model could classify only 32% of the patients as responders or nonresponders with a discriminative ability of 79%. The pharmacogenetic data (the genotypes MTHFD1 1058AA and AMPD1 34CC, and the alleles ITPA 94A and ATIC 347G) introduced into this model improved its ability to predict response to MTX and made it possible to classify 60% of the patients as responders or nonresponders with a discriminative ability of 85%. We will analyze, by means of systematic review, the role of the pharmacogenetics in predicting response to MTX.

Hider, *et al*[11] conducted a literature review similar to ours in 2005. It aimed to identify factors that influence response to different DMARD in RA. They conclude that the strongest predictors of a poor response to treatment are disease duration, previous DMARD use, and poor functional class, the results being similar for MTX and other DMARD, such as sulfasalazine and gold salts. Although female sex is associated with a weaker response to MTX, this association does not seem to be identical for all DMARD. The influence of disease activity at the start of treatment on response to treatment was inconsistent, depending on the study, the DMARD used, and its definition of "response to treatment."

It emerges that the inflammatory disease activity at start of treatment and during followup, ESR, CRP, and positive RF are factors associated with poor radiological prognosis. The predictive factors of radiological progression in patients with RA, especially of recent onset, were searched for in a number of observational studies[11-26]. However, these studies included patients on various DMARD therapies. Since the effect of the different DMARD on radiological damage can differ, it is difficult to conclude whether the factors found in these studies apply to patients treated with MTX. In these studies, anti-CCP emerged as an important predictive factor of more erosive disease[15,21,24]. In one study, anti-CCP tend to be a better radiological prognostic marker than RF[24]. Unfortunately, we found no study that examined this specific factor in patients treated with MTX. In most of the observational studies mentioned above, RF appeared to be a predominant factor for radiological prognosis, although in some of these studies, as in our review, this factor is not independent[15,24]. Unlike our review, certain articles do not show an association between disease activity measured by the DAS and DAS28 at baseline and radiological progression[14-17]. However, most find a link between cumulative disease activity during the followup and joint damage[19,21,24]. Boers, *et al* indicated that the presence of inflammatory signs in a joint predicts damage in that joint[13]. ESR appears to be a better marker than CRP, but the latter is also correlated with joint damage. This association between inflammatory activity and erosive damage was not observed in patients treated with an infliximab/MTX combination, which raises the issue of another mechanism of action for anti-tumor necrosis factor agents on osteoclastic activity, independent of the antiinflammatory effect[5].

Lastly, the analysis by Smolen, *et al*[5] did not show an association between radiological progression and radiological damage at baseline. This is in contrast to most analyses performed with other DMARD, where baseline radiological damage was one of the strongest predictive factors of greater deterioration in the long term.

Our literature review has certain limitations. There were a limited number of reports addressing our specific question, i.e., the predictors of response to MTX monotherapy. Further, most of the studies were not designed to identify the predictors of response as a primary goal of the trial and did not perform power calculation to answer this specific question. As some predictors were assessed in only one or a few studies (the case for anti-CCP), we should be cautious not to generalize these results. We also excluded several articles because they pooled the results for patients who had received various treatments, and other articles because we found that the small number of patients (< 50) did not confer sufficient statistical power to evaluate prognostic factors. Further, the variability in the efficacy measures as well as the statistical tests made it difficult to compare the results in the various articles. We found that a metaanalysis would be inadequate in this context. Consequently, we attempted to report them as faithfully as possible in the tables. Finally, it was impossible to calculate the effect of early withdrawals due to side effects on the identification of predictors of treatment efficacy. Some studies (such as Wessels, *et al*[3]) excluded these patients from the analysis, but most others included them and used the last observation carried forward.

In conclusion, female patients with a positive RF (early arthritis) who smoke and have a high disease activity at baseline are less likely to respond to MTX monotherapy. Further, patients with high disease activity at the start of treatment and in whom activity persists during followup (3 to 6 months) are at greater risk for progression toward radiological damage. However, many of these "high-risk" patients will partially benefit from the treatment, since none of the prognostic factors specifically discriminates between responders and nonresponders. Assessing disease activity at 3–6 months using composite scores such as the DAS28, SDAI, or CDAI seems to be the best clinical method for predicting the longer-term response to MTX.

REFERENCES

1. Hayden J, Côté P, Bombardier C. Evaluation of the quality of prognosis studies in systematic reviews. Ann Intern Med 2006;144:427-37.
2. Rheumatoid Arthritis Clinical Trial Archive Group. The effect of age and renal function on the efficacy and toxicity of methotrexate in rheumatoid arthritis. Rheumatoid Arthritis Clinical Trial Archive Group. J Rheumatol 1995;22:218-23.

3. Wessels JA, van der Kooij SM, le Cessie S, Kievit W, Barerra P, Allaart CF, et al. A clinical pharmacogenetic model to predict the efficacy of methotrexate monotherapy in recent-onset rheumatoid arthritis. Arthritis Rheum 2007;56:1765-75.
4. Hoekstra M, van Ede AE, Haagsma CJ, van de Laar MA, Huizinga TW, Kruijsen MW, et al. Factors associated with toxicity, final dose, and efficacy of methotrexate in patients with rheumatoid arthritis. Ann Rheum Dis 2003;62:423-6.
5. Smolen JS, van der Heijde DM, St. Clair EW, Emery P, Bathon JM, Keystone E, et al. Predictors of joint damage in patients with early rheumatoid arthritis treated with high-dose methotrexate with or without concomitant infliximab: results from the ASPIRE trial. Arthritis Rheum 2006;54:702-10.
6. Rau R, Herborn G, Menninger H, Sangha O. Progression in early erosive rheumatoid arthritis: 12 month results from a randomized controlled trial comparing methotrexate and gold sodium thiomalate. Br J Rheumatol 1998;37:1220-6.
7. Lie E, Heiberg MS, Nordvag BY, Rodevand E, Kaufmann C, Mikkelsen K, et al. Predictors of response to methotrexate treatment: Results from a longitudinal observationnal study of 876 patients with RA [abstract]. Ann Rheum Dis 2006;65 Suppl II:342.
8. Weinblatt ME, Keystone EC, Cohen MD, Freundlich B, Li J, Chon Y, et al. Predictors of poor radiographic response in rheumatoid arthritis subjects treated with methotrexate: preliminary analysis from ERA and TEMPO studies [abstract]. Arthritis Rheum 2006;54 Suppl:S181.
9. Van der Heijde DM, Landewe R, Sharp JT, Bathon J, Patra K, Spencer-Green GT. Baseline CRP concentrations predict radiographic progression in MTX-naive patients with recent-onset RA: Subanalysis of the PREMIER study [abstract]. Ann Rheum Dis 2005;64 Suppl III:436.
10. Aletaha D, Funovits J, Keystone EC, Smolen JS. Disease activity early in the course of treatment predicts response to therapy after one year in rheumatoid arthritis patients. Arthritis Rheum 2007;56:3226-35.
11. Hider SL, Buckley C, Silman AJ, Symmons DP, Bruce IN. Factors influencing response to disease modifying antirheumatic drugs in patients with rheumatoid arthritis. J Rheumatol 2005;32:11-6.
12. Allaart CF, Goekoop-Ruiterman YP, de Vries-Bouwstra JK, Breedveld FC, Dijkmans BA, FARR Study Group. Aiming at low disease activity in rheumatoid arthritis with initial combination therapy or initial monotherapy strategies: the BeSt study. Clin Exp Rheumatol 2006;24 Suppl 43:S-77-82.
13. Boers M, Kostense PJ, Verhoeven AC, van der Linden S, COBRA Trial Group, Combinatietherapie Bij Reumatoide Artritis. Inflammation and damage in an individual joint predict further damage in that joint in patients with early rheumatoid arthritis. Arthritis Rheum 2001;44:2242-6.
14. Combe B, Dougados M, Goupille P, Cantagrel A, Eliaou J, Sibilia J, et al. Prognostic factors for radiographic damage in early rheumatoid arthritis: a multiparameter prospective study. Arthritis Rheum 2001;44:1736-43.
15. Forslind K, Ahlmen M, Eberhardt K, Hafstrom I, Svensson B. Prediction of radiological outcome in early rheumatoid arthritis in clinical practice: role of antibodies to citrullinated peptides (anti-CCP). Ann Rheum Dis 2004;63:1090-5.
16. Garnero P, Landewe R, Boers M, Verhoeven A, van der Linden S, Christgau S, et al. Association of baseline levels of markers of bone and cartilage degradation with long-term progression of joint damage in patients with early rheumatoid arthritis: the COBRA study. Arthritis Rheum 2002;46:2847-56.
17. Kaltenhauser S, Wagner U, Schuster E, Wassmuth R, Arnold S, Seidel W, et al. Immunogenetic markers and seropositivity predict radiological progression in early rheumatoid arthritis independent of disease activity. J Rheumatol 2001;28:735-44.
18. Landewe R, Geusens P, Boers M, van der Heijde D, Lems W, te Koppele J, et al. Markers for type ii collagen breakdown predict the effect of disease-modifying treatment on long-term radiographic progression in patients with rheumatoid arthritis. Arthritis Rheum 2004;50:1390-9.
19. Landewe RB, Boers M, Verhoeven AC, Westhovens R, van de Laar MA, Markusse HM, et al. COBRA combination therapy in patients with early rheumatoid arthritis: long-term structural benefits of a brief intervention. Arthritis Rheum 2002;46:347-56.
20. Lindqvist E, Jonsson K, Saxne T, Eberhardt K. Course of radiographic damage over 10 years in a cohort with early rheumatoid arthritis. Ann Rheum Dis 2003;62:611-6.
21. Machold KP, Stamm TA, Nell VP, Pflugbeil S, Aletaha D, Steiner G, et al. Very recent onset rheumatoid arthritis: clinical and serological patient characteristics associated with radiographic progression over the first years of disease. Rheumatology 2007;46:342-9.
22. Menninger H, Herborn G, Sander O, Blechschmidt J, Rau R. A 36 month comparative trial of methotrexate and gold sodium thiomalate in the treatment of early active and erosive rheumatoid arthritis. Br J Rheumatol 1998;37:1060-8.
23. Sanmarti R, Gomez A, Ercilla G, Gratacos J, Larrosa M, Suris X, et al. Radiological progression in early rheumatoid arthritis after DMARDs: a one-year follow-up study in a clinical setting. Rheumatology 2003;42:1044-9.
24. Sanmarti R, Gomez-Centeno A, Ercilla G, Larrosa M, Vinas O, Vazquez I, et al. Prognostic factors of radiographic progression in early rheumatoid arthritis: a two year prospective study after a structured therapeutic strategy using DMARDs and very low doses of glucocorticoids. Clin Rheumatol 2007;26:1111-8.
25. van der Heijde DM, van Riel PL, van Leeuwen MA, van 't Hof MA, van Rijswijk MH, van de Putte LB. Prognostic factors for radiographic damage and physical disability in early rheumatoid arthritis. A prospective follow-up study of 147 patients. Br J Rheumatol 1992;31:519-25.
26. Vittecoq O, Pouplin S, Krzanowska K, Jouen-Beades F, Menard JF, Gayet A, et al. Rheumatoid factor is the strongest predictor of radiological progression of rheumatoid arthritis in a three-year prospective study in community-recruited patients. Rheumatology 2003;42:939-46.
27. Welsing PM, Landewé RB, van Riel PL, Boers M, van Gestel AM, van der Linden S, et al. The relationship between disease activity and radiologic progression in patients with rheumatoid arthritis: a longitudinal analysis. Arthritis Rheum 2004;50:2082-93.