Radiologic damage at baseline predicts patient-related outcomes 18 years after the initiation of methotrexate therapy in patients with severe rheumatoid arthritis

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Abstract

Objective

We aimed to assess the association of the degree of radiologic damage at baseline with long-term patient-related outcomes (PRO) in patients with severe rheumatoid arthritis (RA)

Methods

This prospective observational single-centre study (Ratingen, Germany) included all RA patients starting treatment with methotrexate (MTX) between 1980 and 1987. Standardised clinical evaluations and radiographs of hands and feet were obtained at baseline and during the following years. About 18 years later, patients were invited for a re-assessment. PRO were assessed in three dimensions according to the International Classification of Functioning and Disability (ICF). Statistical analyses comprised multivariable models using baseline values for radiologic damage of hands and feet, age, gender, disease duration, rheumatoid factor positivity, measures of disease activity, and response to MTX as covariates.

Results

At baseline, the mean disease duration was 8.5 years. The disease was active with a mean number of swollen joints of 18 (out of 32) and a mean erythrocyte sedimentation rate of 55 mm/hour. Radiologic damage was present in 95% of the patients. After 18 years, patient-related outcomes could be assessed in 78/271 patients (29%). Among chosen covariates, only the degree of baseline radiologic damage as measured by the Ratingen score was predictive of all long-term PRO ($p<0.016$).

Conclusion

In this cohort including patients with severe RA, baseline radiologic damage was a good long-term predictor of PRO related to all three ICF dimensions.

Key words

rheumatoid arthritis, methotrexate, radiologic damage, patient outcome assessment

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Introduction

In patients with rheumatoid arthritis (RA), radiologic damage as assessed by plain radiographs of hands and feet (1) is regarded as one of the most important outcome measures (2). During the last years, patient-related outcome measures (PRO) have become more and more important to assess the burden of disease and its impact on activities of daily living. However, in cross-sectional studies, only a weak correlation between radiologic damage and disability in early RA was found (3). In a longitudinal study, joint space narrowing and erosions had no significant effects on physical function in a cohort of patients with recent onset of RA after 5 years of follow-up (4). Because of the rather indirect link between the structural damage of small joints and disability, the significance of radiologic damage in assessing the value of treatments in RA has been challenged (5).

Since the relation between radiologic joint damage and the long-term course of PRO has not been extensively studied to date, we analysed the data of our cohort in Ratingen that included all patients who had started treatment with methotrexate (MTX) between 1980 and 1987 (6, 7). Baseline characteristics and response to MTX treatment after one year had been assessed. According to the three dimensions of outcome of disease proposed by the International Classification of Functioning and Disability (ICF) (body functions and structure, activities at the individual level, and participation in society) (8), the following PROs were chosen: number of large joints with limited motion for the dimension "body functions and structure", self-reported physical functioning for the dimension "activities at the individual level", and self-sufficiency for the dimension "participation in society".

Materials and methods

Patient characteristics

All patients with RA (9) who started MTX treatment in the Department of Rheumatology, Evangelisches Fachkrankenhaus Ratingen, Germany, between January 1, 1980 and December 31, 1987 were enrolled in this prospective study. Patients gave informed consent and all procedures were in accordance with the ethical standards of the Helsinki Declaration of 1975, as revised in 1983.

All patients had active disease and had been treated with at least one other disease-modifying anti-rheumatic drug (DMARD). MTX was usually given intravenously or intramuscularly in dosages of 15–25 mg/week. Most patients changed from parenteral to oral medication after a few months. Patients were allowed to continue treatment with non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, or previous DMARD, if these were well tolerated and subjectively regarded as being effective.

Clinical assessments

Standardised clinical evaluations were performed at baseline and follow-ups. As described (10), response to treatment was evaluated one year after baseline and rated as ≥20% improvement or <20% improvement. Patients who discontinued MTX treatment within the first year made up a third group.

In 2003, a systematic re-evaluation of patients included in this study was performed. Patients were questioned about self-sufficiency (0 = self-sufficient, 1 = dependent on others for help). Furthermore, self-reported physical functioning was estimated using a German questionnaire (Funktionsfragebogen Hannover) that is closely correlated to the health assessment questionnaire (HAQ) (11). The results of these questionnaires can be transformed mutually. In addition, a complete physical examination was performed, including a swollen joint count (SJC) as well as assessment of joint deformities and range of joint motion. Deformities were defined as subluxation or luxation, contracture, or ankylosis. In more detail, 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, forefeet deformities were recorded. Reduction of motion by more than one third of the normal range was rated as abnormal and was labelled "limited motion". A 38-joint-count was performed that included proximal inter-

phalangeal and metacarpophalangeal joints, wrists, elbows, shoulders, knees, ankles, and metatarsophalangeal joints II–V. A second joint count comprised only ten large joints (wrists, elbows, shoulders, knees, and ankles).

Radiologic assessments

Radiographs were taken at baseline and after one year. Most patients had radiographic follow-up examinations available. Radiographs were centrally evaluated and read by one observer (RR or GH), who was unaware of the patients' history and treatment. Radiographs of hands and feet were analysed using the Ratingen score (12). This scoring method evaluates a total of 38 joints graded on a 0–5 scale according to the amount of joint surface destruction (range of scores 0–190) without grading joint space narrowing.

Statistical analysis

Multiple regression analysis was performed for the number of large joints with limited motion (out of 10) at 18 years after baseline. Baseline radiologic damage of hands and feet, baseline values of age, gender, disease duration, rheumatoid factor (RF) positivity, SJC, ESR, and patient global assessment, response to MTX treatment after one year, and deterioration of radiologic damage in the first year and in the following years were used as covariates. The same analysis was performed for self-reported physical functioning 18 years after baseline. Using the same covariates, we finally did logistic regression for self-sufficiency. With regard to multiple testing, *p*-values less than 0.016 were considered significant according to the Bonferroni procedure.

Secondary analysis comprised multiple regression for the 38 joint count regarding deformities, limitation of motion, or operations, respectively. Because of the direct link of the Ratingen score with 30 (proximal interphalangeal and metacarpophalangeal joints, wrists, and metatarsophalangeal joints II-V) of these 38 joints, these analyses were regarded as secondary and no adjustment for multiple testing was done.

SAS, version 9.2 (SAS Institute, Cary, NC) was used for statistical analysis.

Table I. Predictors of the number of large joints (wrists, elbows, shoulders, knees, ankles) with limited motion 18 years after baseline.

Variable	Parameter estimate	Standard error	*p*-value
Age at baseline	0.1247	0.0887	0.1646
Female gender	-0.0740	1.9686	0.9701
Disease duration	0.2575	0.1642	0.1217
Rheumatoid factor positivity at baseline	0.4091	2.2912	0.8588
Swollen joint count at baseline	0.1197	0.1045	0.2562
ESR at baseline	0.0171	0.0292	0.5617
Patient global assessment at baseline	0.3756	1.8150	0.8367
<20% improvement one year after baseline	1.2603	0.7860	0.1137
Ratingen score at baseline	0.0575	0.0229	0.0144
Increase in Ratingen score within the first year	-0.0808	0.1326	0.5445
Annual increase in Ratingen score after the first year	0.3417	0.2793	0.2256

ESR: erythrocyte sedimentation rate.

Results

Patient characteristics at baseline

A total of 271 consecutive patients with definite RA were included in the study between January 1, 1980 and December 31, 1987. The mean age was 58 years, the mean disease duration 8.5 years, and 95% of the patients had joint erosions. Patients had active disease at baseline with a mean number of swollen joints of 18 (out of 32) and a mean ESR of 55 mm/hour. Almost all patients took NSAIDs (96%), and 169 (62%) took prednisone (mean dosage of 4.5 mg/day). Nearly all patients rated their global disease activity as severe.

Treatment and response after one year

Sevety-nine patients (29%) were treated with MTX after previous DMARD treatment had been discontinued. In the remaining patients, MTX was used as add-on therapy together with other DMARDs (*e.g.* parenteral gold, D-penicillamine or chloroquine).

After one year of MTX treatment, 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

147 patients (54%) had died during the 18 years after baseline, 14 patients (5%) could only be interviewed by telephone, and 21 patients (8%) were lost to follow-up. Thus, patient-related outcome could be assessed in 89 out of 271 patients (33%), but 11 patients (4%) had incomplete radiologic data at baseline. Therefore, the cohort that was finally available for statistical analyses comprised a total of 78 patients (29%).

Using multiple regression analysis, the only significant predictor of the number of large joints with limited motion 18 years after baseline was the degree of radiographic damage at baseline as quantified by the Ratingen score, while no significant association was found for baseline values of age, gender, disease duration, RF positivity, ESR, SJC, patient global assessment, or response to MTX treatment after one year. Furthermore, the annual increase in Ratingen score after baseline was not predictive of joint deformities 18 years later (Table I).

Similar results were found for self-reported physical functioning. There was an association of age and baseline radiographic score of hands and feet (Ratingen score) with self-reported physical functioning after 18 years of follow-up (Table II). No significant association with limited motion was found for gender, disease duration, disease activity at baseline, global assessment at baseline, or response to MTX treatment. Radiologic deterioration in the following years had no significant influence on the limitation of motion in large joints.

Self-sufficiency after 18 years of follow-up showed correlations with age, RF positivity, response to MTX treatment, and Ratingen score at baseline (Table III).

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

Variable	Parameter estimate	Standard error	*p*-value
Age at baseline	-1.1670	0.3719	0.0026
Female gender	-10.0822	7.8287	0.2026
Disease duration	-0.1886	0.6424	0.7701
Rheumatoid factor positivity at baseline	-4.7756	9.0544	0.5998
Swollen joint count at baseline	-0.4373	0.4092	0.2893
ESR at baseline	-0.0927	0.1203	0.4440
Patient global assessment at baseline	-0.5139	7.2255	0.9435
<20% improvement one year after baseline	-7.4793	3.1245	0.0197
Ratingen score at baseline	-0.2436	0.0899	0.0087
Increase in Ratingen score within the first year	1.3385	0.7081	0.0634
Annual increase in Ratingen score after the first year	-1.6372	1.1144	0.1469

ESR: erythrocyte sedimentation rate.

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

Variable	Odds ratio	95% confidence intervall	*p*-value
Age at baseline	0.837	0.738-0.949	0.0056
Female gender	1.888	0.270-13.196	0.5217
Disease duration at baseline	0.914	0.782-1.070	0.2644
Rheumatoid factor positivity	0.081	0.007-0.963	0.0466
Swollen joint count at baseline	1.022	0.929-1.124	0.6530
ESR at baseline	1.005	0.975-1.035	0.7661
Patient global assessment at baseline	0.244	0.036-1.657	0.1490
<20% improvement one year after baseline	0.379	0.167-0.860	0.0202
Ratingen Score at baseline	0.970	0.947-0.993	0.0104
Increase in Ratingen Score in the first year	1.033	0.931-1.147	0.5396
Annual increase in Ratingen score after the first year	1.068	0.833-1.369	0.6027

ESR: erythrocyte sedimentation rate.

The secondary analysis of the 38-joint score (proximal interphalangeal and metacarpophalangeal joints, wrists, elbows, shoulders, knees, ankles, and metatarsophalangeal joints II-V) again showed an association with baseline Ratingen score, but – except for a correlation of age with the number of operated joints – no other meaningful associations with baseline values, disease duration, or response to MTX treatment could be found (Table IV).

Discussion

RA is a chronic inflammatory rheumatic disease that may affect patients' physical functioning, ability to work, and quality of life. Since most randomised controlled clinical trials are of relatively short duration, long-term studies such as our present one are of major interest – especially given the relative paucity of good long-term data. On the background of a rather special selection of patients with very severe disease in those early days when methotrexate was just beginning to be studied in rheumatology, our data show that the degree of radiologic damage at baseline was the only predictor of PRO in all three dimensions – an outcome parameter of rather increasing significance – assessed 18 years later.

Radiologic damage has become a cornerstone in the assessment of efficacy of therapeutic interventions in RA in the last decade – especially due to the strong effect of biologics on structural outcomes. This finding clearly backs the concept that radiologic damage does not only mirror the clinical damage caused by the preceding inflammatory process but also predicts the future destructive tendency of the disease. This seems relevant since this conception was recently questioned because in cross-sectional (3) and in longitudinal studies (4) only a weak association of radiologic damage and disability was found in patients with early RA – a finding which seems to be most probably explained by the relatively lower incidence and prevalence of osteodestructive changes in early disease stages and, again, the strong potency of biologics to prevent such changes to occur.

In this post-hoc analysis of data obtained in a prospective single-centre observational trial, we decided, guided by the ICF (8), to choose PRO in three dimensions of disease outcomes: body functions and structure, activities at the individual level, and participation in society. As damage of large joints is thought to be an important predictor of disability (3), the number of large joints (wrists, elbows, shoulders, knees, and ankles) with limited motion was selected as PRO for the dimension "body functions and structure". For the second dimension ("activities at the individual level") self-reported physical functioning has emerged as an established tool in daily rheumatology practice. The third dimension ("participation in society") is reflected by self-sufficiency. For all PRO assessed 18 years after baseline, a significant association with baseline radiologic damage of hands and feet, as assessed by the Ratingen score, was found. Measures of disease activity at baseline or disease duration at baseline had no impact on these PRO after 18 years. The Ratingen score has been compared with the more frequently used van der Heijde/Sharp-score and performed equally well (13).

The secondary analysis showed a strong association of baseline radiologic damage of hands and feet with the number of joints with limited range of motion, deformities, or operations 18 years after baseline. The link between baseline radiologic damage and long-term clinical damage of the involved joints is intuitive. The link between a radiologic score and joints not included in this score is weaker and more indirect. Even more indirect is the connection of a radiologic score with self-reported physical functioning or self-sufficiency. It has been shown that the link between radiologic damage and physical functioning is weak in early RA, but becomes more obvious with increasing disease duration (by 5–8 years), being strongest after 12 years (13, 14). In late

Table IV. Predictors of limited motion, deformities, operation of 38 joints (multiple regression).

Variable	Limited motion		Deformities		Operation	
	Parameter estimate (SE)	*p*-value	Parameter estimate (SE)	*p*-value	Parameter estimate (SE)	*p*-value
Age at baseline	0.1521 (0.1564)	0.3344	0.1636 (0.1298)	0.2117	-0.0273 (0.0883)	0.7586
Female gender	-1.4434 (3.4802)	0.6797	1.1944 (2.8866)	0.6804	4.0559 (2.0265)	0.0495
Disease duration	0.5602 (0.2897)	0.0575	0.4214 (0.2403)	0.0841	0.1681 (0.1633)	0.3072
Rheumatoid factor positivity	0.3871 (4.0502)	0.9242	0.6601 (3.3593)	0.8448	1.9066 (2.2884)	0.4078
Swollen joint count at baseline	0.3511 (0.1821)	0.0581	0.2163 (0.1510)	0.1568	0.0138 (0.1029)	0.8938
ESR at baseline	0.0186 (0.0516)	0.7193	0.0398 (0.0428)	0.3563	-0.0102 (0.0291)	0.7280
Patient global assessment at baseline	0.2386 (3.2049)	0.9409	-0.8876 (2.6582)	0.7395	-2.4644 (1.8069)	0.1773
<20% improvement one year after baseline	1.0698 (1.3807)	0.4412	0.9571 (1.1452)	0.4063	0.0013 (0.7787)	0.9987
Ratingen Score at baseline	0.1006 (0.04014)	0.0146	0.0917 (0.0333)	0.0076	0.0645 (0.0226)	0.0059
Increase in Ratingen Score in the first year	-0.1820 (0.2342)	0.4400	0.0121 (0.1943)	0.9505	-0.0833 (0.1325)	0.5319
Annual increase in Ratingen score after the first year	0.5099 (0.4935)	0.3053	0.1146 (0.4093)	0.7804	0.0992 (0.2808)	0.7276

SE: standard error; ESR: erythrocyte sedimentation rate; 38 joints: proximal interphalangeal and metacarpophalangeal joints, wrists, elbows, shoulders, knees, ankles, and metatarsophalangeal joints II-V.

RA, small joint involvement in radiologic damage is closely associated with large joint involvement and this in turn is associated with functional disability (15). In a recent study, this link of greater radiologic damage and a higher degree of disability could be observed as early as 2 years after baseline (16). In general, the impact of disease activity and joint destruction on physical functioning changes over the course of the disease. Whereas in early RA, functional capacity is primarily associated with disease activity, the association with joint damage is stronger in the later course (17) and independent of the ESR as a marker of disease activity (18). With these studies, the concept of a close link between radiologic damage and impaired PRO may be regarded as proven in late RA stages.

Regarding the predictive value of radiologic damage assessment concerning PRO in the course of RA, several studies have shown associations of baseline radiologic joint damage and physical functioning after one year (19), 5 years (20), and a mean of 6.7 years (21). In our study, this association remained obvious even after a mean of 18 years. Moreover, this association was not only evident for the dimension of activities at the individual level, but also for the other two disease outcome dimensions ("body functions and structure" as well as "participation in society").

A weakness of this study is the relatively small number of patients which may not be so surprising given the time when it started, the severity of the disease, and the length of the study. Nonetheless, the link between radiologic damage and PRO in late RA seems to be strong enough to yield significant results even with small numbers of patients.

Another weakness of our study is the paucity of PRO assessments at baseline. Only patient global assessment was recorded, but that was not predictive in our analysis. This is due to the fact that nearly all patients rated the highest level ("severe") of the four point Likert scale. The assessment of PRO is an established tool in predicting outcomes in RA, especially regarding mortality (22). Thus, how much of the predictive value of radiologic damage at baseline would have been revealed by assessment of PRO at baseline – including functional status and health-related quality of life (23) – remains unclear.

Due to the observational character of this study, the results may rather be considered hypothesis generating. The fact that most patients in this study had rather advanced disease at baseline may obviously limit the relevance of our results for patients treated according to modern treatment strategies who may never get to the late disease stage that many of our patients were in when entering the study.

In conclusion, in our unique cohort baseline radiologic damage predicted PRO after 18 years in all three ICF dimensions. This finding strengthens the importance of radiologic evaluation of joint damage at hands and feet for treatment decisions in RA. But of course, these data refer to long-standing disease, and the relationship may be lost in patients with early RA.

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