Response to methotrexate predicts long-term mortality of patients with rheumatoid arthritis independent of the degree of response: results of a re-evaluation 30 years after baseline

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Abstract

Objective

To assess if there is a correlation between the degree of response to treatment with methotrexate (MTX) and long-term mortality in a cohort of patients with rheumatoid arthritis (RA) established in Germany in the early eighties.

Methods

RA patients who had started MTX treatment between 1980 and 1987 were included. One year after baseline, the treatment response was evaluated. Responders were defined as patients with at least 20% decline in the swollen joint count (out of 32 joints) and the ESR with a prednisone dosage <5 mg/day. Thereafter, assessments were performed at 10, 18, and 30 years after baseline. Standardised mortality ratios (SMR) were calculated, Cox regression and logistic regression were performed.

Results

The cohort comprised 271 patients. In 2015, about 30 years after the initiation of MTX therapy, 185 patients (68%) were deceased, 52 (19%) lost to follow-up and 34 alive. The response after the first year of MTX treatment was the strongest predictor of survival with a hazard ratio of 0.44 (95% confidence interval [CI]: 0.30-0.65). However, even responders still had an SMR of 1.37 (95% CI 1.31–1.65), but this was much worse for non-responders who had an SMR of 4.22 (95% CI 3.13–5.56). Using Cox regression analysis no difference was detected between responders with more than 50% improvement (38% of all patients) and those with 20–50% improvement (28%).

Conclusion

The predictive value of a response to one year of MTX therapy for long-term mortality of RA patients is independent of the degree of response.

Key words

rheumatoid arthritis, methotrexate, long-term outcome, mortality

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Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune disease leading to joint inflammation (1). Without sufficient treatment, irreversible bone and cartilage erosions may evolve, causing deformities and impairment (2, 3). Patients with RA show elevated mortality rates in comparison to the general population (4, 5). Reduced life expectancy was found to be associated with higher age, male gender, comorbidities and poor functional capacity (6, 7). In particular, high disease activity seems to contribute to increased mortality (8).

Methotrexate (MTX), a conventional disease-modifying anti-rheumatic drug (DMARD), is considered to be the "anchor drug" in the treatment of RA (9). Early treatment with MTX can provide a survival benefit, especially by reducing cardiovascular mortality (10). The impact of MTX on disease activity is believed to account for this effect. However, RA patients with insufficient response to MTX still profited from the continuation of MTX treatment and showed an improved outcome (11).

The degree of response to DMARDs is considered to be correlated to functional outcome. Recently, this concept led to a new definition of remission by the American College of Rheumatology and the European League Against Rheumatism predicting good functional outcome in 80% of RA patients fulfilling these criteria (12). In order to assess whether a similar correlation exists between the degree of treatment response and long-term mortality, we re-evaluated one of the oldest MTX cohorts of RA patients in Europe, established by Rolf Rau in Ratingen, Germany, in the early eighties.

Materials and methods

Patients and procedures

All RA patients with a high disease activity, who had failed to respond to at least one other conventional DMARD, such as gold or sulfasalazine, and started treatment with MTX between January 1, 1980 and December 31, 1987, were enrolled in a prospective observational study. MTX was administered intravenously or intramuscularly in dosages of 15–25 mg/week, but usually changed to oral medication after a few months. If the previous DMARD was regarded as somewhat effective, patients were allowed to continue this DMARD at full dosage together with MTX.

A swollen joint count in 32 joints (SJC32) was used comprising the proximal interphalangeal and metacarpophalangeal joints, wrists, elbows, shoulders, knees, ankles as well as the metatarsophalangeal joints II-V rated as one joint per foot. Comorbidities were classified using the Charlson score (13). Patients rated their global disease activity on a four point Likert scale (range 0 to 3).

One year after baseline, the response to MTX treatment was evaluated. The rates of improvement were graded as >50%, 20–50% improvement or <20% improvement. Improvement of >50% was defined as a >50% decrease in the SJC32 as well as in the erythrocyte sedimentation rate (ESR) in comparison to baseline. Respectively, improvement of 20–50% was defined as a 20-50% decline in the SJC32 and ESR. In both definitions, the mean prednisone dosage had to be <5 mg/day. Patients who had discontinued treatment with MTX due to side effects such as nausea or stomatitis made up a fourth group.

In 1995, 2003 and 2015 re-evaluations were performed. They included the assessment of swollen and tender joints as well as joint deformities. In addition, patients were questioned about self-sufficiency and self-reported physical functioning was recorded.

This study has been conducted following all ethical standards according to the Helsinki Declaration of 1975. For this last follow-up, the study protocol and the informed consent document were reviewed and approved by the ethics committee of the University of Muenster, Germany (registration number 2015-333-f-S). All patients provided written informed consent before participating. The study was registered at the German register for clinical studies (DRKS) and at clinicaltrials.gov.

Statistical analysis

Standardised mortality ratios (SMRs) were assessed as the ratio of the observed number of deaths in the study

Table I. Baseline characteristics of patients according to response groups one year after baseline (n=271).

Characteristic	>50% improvement	20-50% improvement	<20% improvement	Discontinued treatment	Total
Patients, no. (%)	102 (37.6)	75 (27.7)	56 (20.7)	38 (14.0)	271(100)
Women, %	81.4	84.0	67.9	84.2	79.7
Age, years	56.0±10.8	56.7±10.3	58.6±10.0	62.3±9.8	57.6±10.5
RF positive status, %	86.3	88.0	91.1	81.6	86.7
Disease duration, years	8.4±7.5	8.4±6.4	8.6±6.8	8.5±6.5	8.5±6.9
Charlson score	0.44±0.74	0.48±0.66	0.59±0.73	1.00 ± 1.07	0.56±0.79
PGA (range 0-3)	2.78 ± 0.46	2.89±0.31	2.77±0.50	2.79±0.53	2.81±0.44
SJC32	18.4±7.5	18.6±7.1	15.7±7.2	17.9 ± 6.9	17.8±7.3
ESR, mm/hour	54.9±29.2	52.8±29.5	57.3±31.1	65.2 ± 37.8	56.3±31.1

Values are mean ± SD unless otherwise indicated. RF: rheumatoid factor; SJC32: swollen joint count in 32 joints; ESR: erythrocyte sedimentation rate; Charlson score: comorbidity score; PGA: patient global assessment of disease activity.

group to the expected number of deaths in the general population in an age and sex matched sample using the mortality charts of Western Germany (14). Probability of survival was depicted as a function of time by using the Kaplan-Meier estimator. Significance of differences between the groups was determined by the log-rank test with *p*-values <0.05 considered as significant.

Hazard ratios for death of patients with ≥20% improvement one year after baseline were compared to those with <20% improvement after adjusting for the baseline values of age, gender, disease duration, Charlson comorbidity score, rheumatoid factor (RF), SJC32 and ESR. Furthermore, hazard ratios for death of patients with >50% improvement were compared to those with 20-50% improvement with adjustments for the above mentioned factors. Sensitivity analysis was made.

To assess whether any patient characteristic had promoted remission, logistic regression was done using age, gender, disease duration, Charlson score, RF positivity, SJC32, ESR and patient's assessment of disease activity as covariates.

SAS, v. 9.4 (SAS Institute, Cary, NC) was used for the statistical analyses.

Results

Patient characteristics at baseline

271 RA patients were included in this study between 1980 and 1987 with a mean age of 58 years and a mean disease duration of 8.5 years. 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: 56 mm/h). All patients had received at least one other conventional DMARD without sufficient response. Additionally, 96% of the patients took non-steroidal anti-inflammatory drugs and 62% took prednisone (with a mean dosage of 4.5 mg/day). Nearly all patients rated their global disease activity as severe (with a mean of 2.8 on a four-point Likert Scale from 0 to 3) (Table I).

Treatment and response after one year

One year after baseline, almost 38% of the patients showed >50% improvement (Table I) with a mean SJC32 of 4.4 and a mean ESR of 22.2 mm/h. 28% of the patients improved more than 20%, but less than 50%. They had a mean SJC32 of 10.6 and a mean ESR of 32.0 mm/h, while 21% of the patients did not improve ≥20% compared to baseline under treatment with MTX, with a mean SJC32 of 14.4 and a mean ESR of 48.6 mm/h.

38 patients (14%) had discontinued treatment with MTX within the first year due to side effects, such as nausea, vomiting or stomatitis. Those patients were not included into further analyses.

Patient evaluation 30 years after baseline

Follow-ups were performed 10, 18 and 30 years after baseline. Until 2015, at average 30 years after baseline, 185 patients were deceased (68%), while 52 patients (19%) had been lost to follow-up, leaving 34 patients for further examination (Fig. 1). This resulted in an overall SMR of 1.89 (95% confidence interval [95% CI] 1.64–2.18). Patients who had discontinued MTX within the first year after baseline had an SMR of 4.16 (95% CI 2.84–5.90) compared to 1.72 (95% CI 1.47–2.01) for those patients who had continued MTX treatment for at least one year.

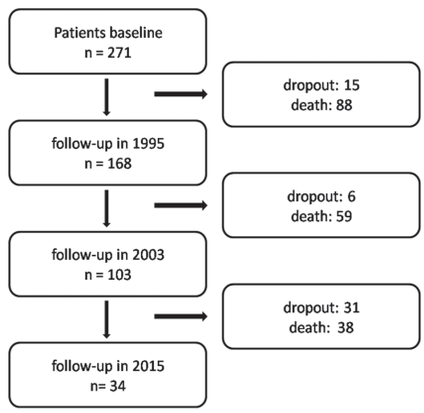

Fig. 1. Flow chart of patients enrolled.

Of all known causes of death (n=113), the leading cause were cardiovascular diseases (50.4% of all deceased patients with a known cause of death), followed by cancer (14.2%), gastrointestinal diseases (8.8%), cachexia (8.8%), pneumonia (7.1%), septicaemia or infection (4.4%), renal failure (3.5%), suicide (0.9%), atlanto-dental dislocation (0.9%) and craniocerebral injury (0.9%).

Remarkable differences in mortality could be found between the groups of different improvement after one year of continued MTX treatment. While the SMR for the group of so-called responders, including patients with >50% improvement as well as 20–50% improvement, was 1.37 (95% CI 1.31–1.65), patients with less than 20% improvement, classified as non-responders, showed an SMR of 4.22 (95% CI 3.13–5.56). Most patients went on with MTX treatment after the first year. Due to a lack of other efficacious DMARDs in the early eighties, even in the group with less than 20% improvement MTX use was continued if it was regarded as somewhat effective.

Figure 2 shows the plots of Kaplan-Meier product-limit estimates of survival, which indicates a significantly longer life expectancy for patients who responded to MTX treatment with ≥20% improvement compared to those patients who continued to take MTX but did not show a response of at least 20%. The difference was significant in the log-rank test (p<0.001).

Younger age, a low Charlson score for comorbidities, minor patient assessment of disease activity and response, defined as ≥20% improvement after one year of treatment with MTX, had a positive impact on survival in both, the univariable and multivariable Cox regression of the patients who had continued MTX intake for at least one year (n=233). Female gender showed a positive impact in the multivariable analysis, but not in the univariable analysis, whereas ESR was a significant predictor in the univariable, but not in the multivariable analysis. With a hazard ratio (HR) of 0.44 (95% CI 0.30–0.65) in the multivariable analysis, response to MTX treatment appears to be the strongest predictor for a prolonged survival (Table II). When restricting our analyses to those patients still alive in 1995, inclusion of "continuation of MTX treatment until 1995" as a covariate led to a HR for MTX response of 0.54 (95% CI 0.30–0.95) in the multivariable analysis (n=155).

The logistic regression for predicting response to MTX treatment from the baseline values (age, gender, Charlson score, disease duration, RF positivity, SJC32, ESR and patient global assessment) found significant results only for female gender (odds ratio 0.39, 95% CI 0.19–0.81) and SJC32 (odds ratio 0.95, 95% CI 0.91–0.99).

The probability of survival did depend on response but not on the degree of response to MTX treatment. This is indicated by the Kaplan-Meier estimator of the probability of survival in patients with more than 50% improvement and in patients with 20-50% improvement (Fig. 2). Patients with more than 50% improvement after one year of treatment with MTX had no survival benefit in comparison to patients with 20–50% improvement.

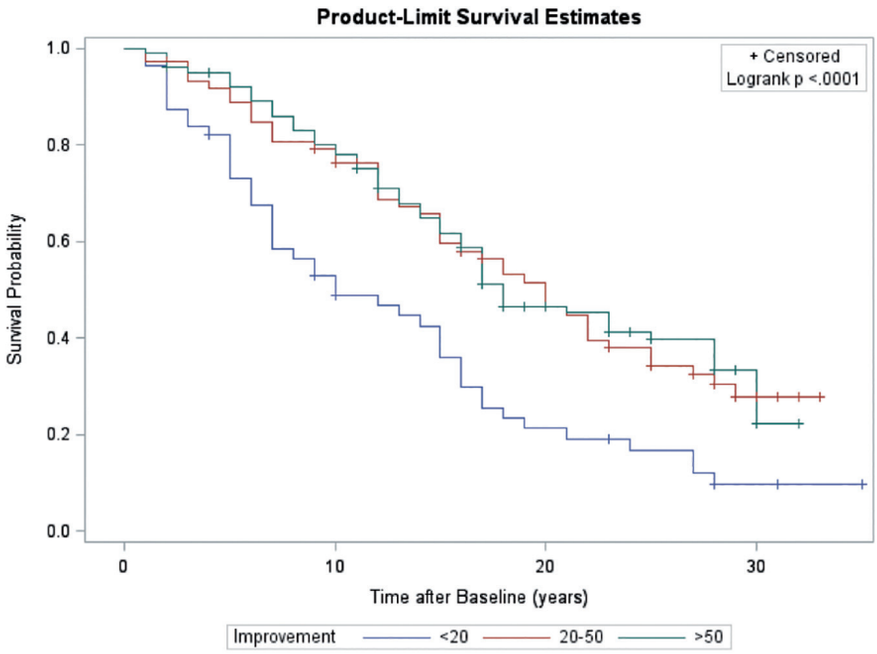

Fig. 2. Kaplan-Meier plot of the probability of survival for patients with >50% improvement, with 20-50% improvement and with <20% improvement after one year of treatment with MTX. There is no significant difference in probability of survival between patients with >50% improvement and patients with 20-50% improvement. Although, the difference in probability of survival is significant between patients with <20% improvement and patients with 20-50% or >50% improvement.

Table II. Cox regression analysis predicting long-term mortality from multiple baseline variables and response to methotrexate one year after baseline in patients who continued methotrexate treatment for at least one year (n=233).

Characteristic	Univariable analysis		Multivariable analysis	
	HR (95% CI)	p	HR (95% CI)	p
Age per year	1.10 (1.08-1.11)	<0.001	1.10 (1.07-1.120)	<0.001
Female gender	0.80 (0.56-1.15)	0.233	0.66 (0.45-0.99)	0.042
Charlson score	1.89 (1.53-2.32)	<0.001	1.39 (1.09-1.76)	0.007
Disease duration	1.00 (0.98-1.03)	0.924	1.01 (0.98-1.03)	0.693
RF positive status	1.47 (0.85-2.55)	0.167	1.41 (0.80-2.48)	0.242
SJC 32	1.01 (0.99-1.04)	0.220	1.02 (1.00-1.04)	0.111
ESR	1.01 (1.00-1.01)	0.002	1.01 (1.00-1.01)	0.057
PGA (range 0-3)	1.75 (1.14-2.70)	0.011	1.71 (1.10-2.67)	0.018
MTX response	0.48 (0.34-0.68)	<0.001	0.44 (0.30-0.65)	<0.001

Charlson score: comorbidity score; RF: rheumatoid factor; SJC32: swollen joint count in 32 joints; ESR: erythrocyte sedimentation rate; PGA: patient global assessment of disease activity; MTX response: ≥20% improvement to methotrexate treatment after one year.

Accordingly, the Cox regression of the group of responders (n=177) showed a positive impact on survival for younger age in both, the univariable and multivariable analysis, whereas a low Charlson comorbidity score, low SJC32 and low ESR were significant predictors of survival only in univariable models. More than 50% improvement after one year of MTX treatment (compared to 20–50% improvement) had neither significant impact in the univariable (HR 0.98, 95% CI 0.67–1.44) nor in the multivariable model (HR 0.92, 95% CI 0.62–1.36) (Table III).

In order to provide some insights into the effects of possible confounders for the last finding, we repeated the multivariable Cox regression of the group of responders with some modifications. First we rated the time of censoring as time of death (n=177), which rendered a HR of 0.92 (95% CI 0.63–1.36) for the improvement of >50% (compared to 20-50% improvement). Next we added the radiologic findings at base-

Table III. Cox regression analysis predicting long-term mortality from multiple baseline variables and >50% improvement to methotrexate one year after baseline in patients with response after one year of continued methotrexate treatment (n=177).

Characteristic	Univariable analysis		Multivariable analysis	
	HR (95% CI)	*p*	HR (95% CI)	*p*
Age per year	1.11 (1.09-1.14)	<0.001	1.11 (1.08-1.14)	<0.001
Female gender	0.96 (0.59-1.54)	0.851	0.64 (0.39-1.07)	0.086
Charlson score	1.74 (1.34-2.24)	<0.001	1.27 (0.96-1.67)	0.091
Disease duration	1.00 (0.97-1.03)	0.849	1.01 (0.98-1.04)	0.609
RF positive status	1.46 (0.79-2.73)	0.231	1.49 (0.77-2.86)	0.232
SJC 32	1.03 (1.00-1.05)	0.030	1.03 (1.00-1.06)	0.116
ESR	1.01 (1.00-1.01)	0.021	1.01 (1.00-1.01)	0.062
PGA (range 0-3)	1.77 (1.00-3.15)	0.052	1.14 (0.63-2.05)	0.667
>50% MTX response	0.98 (0.67-1.44)	0.927	0.92 (0.62-1.36)	0.679

HR: hazard ratio; 95% CI: 95% confidence interval; Charlson score: comorbidity score; RF: rheumatoid factor; SJC32: swollen joint count in 32 joints; ESR: erythrocyte sedimentation rate; PGA: patient global assessment of disease activity; >50% MTX response: >50% improvement to methotrexate treatment after one year.

line (Larsen score) (n=132) as a covariate to the multivariable model; this resulted in a HR of 1.01 (95% HR 0.62–1.65) for >50% improvement. Then, we additionally adjusted for continued MTX use until 1995 (n=130); this yielded a HR of 0.96 (95% CI 0.59–1.56) for >50% improvement (compared to 20-50% improvement). Thus, the finding of comparable mortality rates in both responder subgroups persisted.

Discussion

Patients with RA show elevated mortality rates in comparison to the general population, with cardiovascular diseases being the leading attributed cause of death (15). In this post-hoc analysis of a historical prospective observational single center study of RA patients with a mean follow-up of 30 years, the SMR was 1.89. This is comparable to a mean SMR of 1.74 that was calculated using data of 19 clinic-based non-inception cohorts (7). A recently reported Spanish incident RA cohort with a maximum follow-up of 20 years had the same SMR as our cohort (16). Younger cohorts showed lower SMRs, *e.g.* 1.22 as reported from the Norfolk Arthritis Register (NOAR) (17).

According to the data of NOAR, mortality rates have not improved over the past 20 years compared to the general population, although a Swedish study found a yearly decrease of 3.7% for RA as the underlying cause of death in the years 1997-2013 (18). Leading causes of death in RA patients remain cardiovascular diseases, cancer (19) and respiratory diseases (19, 20). This also applies to our patients with cardiovascular diseases being the underlying cause of death in more than 50% of patients with an identified cause of death. In our study, younger age, low Charlson score for comorbidities and minor patient global assessment of disease activity had a positive impact on mortality, whereas RF positive status had an HR of 1.41, but did not reach significance (95%CI 0.80–2.48). A study from the Netherlands showed that comorbidities, especially cardiovascular diseases, respiratory diseases, cancer and depression had an influence on survival (21). RF positive status was not only a significant risk factor for mortality in the data of the NOAR but also in other studies (22, 23).

In this cohort, MTX treatment led to an improvement of ≥20% in 66% of patients after one year. Our data suggests that this response is a strong predictor for a prolonged survival, with a HR of 0.44 (95%CI 0.30-0.65) after adjusting for age, gender, disease duration, comorbidity, RF positivity, signs of baseline disease activity such as SJC and ESR, and baseline patient global assessment. Patients with ≥20% improvement after one year of MTX treatment, so called responders, showed an SMR of 1.37 in contrast to an SMR of 4.22 for MTX non-responders. A positive effect of early response to DMARD treatment on long-term functional outcome was also seen in a French cohort (24).

In our cohort, however, the degree of MTX response did not modify life expectancy. Patients with more than 50% improvement and those with 20-50% improvement after one year of treatment with MTX had similar survival rates. This is comparable to a result of the FIN-RACo study that investigated the association of the degree of response to DMARD treatment after two years with the amount of work capacity up to 5 years after baseline. A positive effect was seen for patients with an ACR20 and an ACR50 response in comparison to non-responders, but not between patients in the ACR20 and ACR50 response groups (25).

The factors causing MTX response in RA patients are not fully understood. In a Swedish study, clinical predictors of poor response to MTX treatment were current smoking, female sex, longer symptom duration and younger age (26). Also pharmacogenetic and pharmacogenomic characteristics may trigger MTX response in RA patients (27, 28). In our cohort, male gender and a low SJC32 at baseline promoted MTX response as measured by relative improvement to baseline values.

Thus, our results indicate that MTX response after the first year of treatment is associated with low long-term mortality. Although, a high degree of MTX response does not provide additional advantages concerning long-term mortality of RA patients.

There are limitations of this study. 19% of our patients were lost to follow-up; this percentage is comparable to other long-term studies (29). Because of the long disease duration and the high percentage of patients with erosions at baseline our findings may not be representative for other cohorts of RA patients. Furthermore, since our cohort was established in the early eighties, when there were no biologic agents available, the RA treatment of our cohort differed from the treatment of recently diagnosed RA cohorts. As in observational trials describing long-term mortality outcomes, confounding by indication cannot be ruled out.

With these limitations, our results demonstrate the positive long-term impact of MTX response on mortality. Even if RA patients fail to reach a high-grade MTX response, they may still benefit from a state of low disease activity regarding life expectancy.

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