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

D. Krause[1], B. Gabriel[2], G. Herborn[3], J. Braun[4], R. Rau[3]

[1]Rheumatology private office, Gladbeck, Germany, and Department of Medical Informatics, Biometry and Epidemiology, Ruhr-University, Bochum, Germany; [2] Primary care office, Gladbeck, Germany; [3]Department of Rheumatology, Evangelisches Fachkrankenhaus, Ratingen, Germany; [4]Rheumazentrum Ruhrgebiet, Herne, Germany.

Abstract

Objective

Methotrexate (MTX) is the anchor drug in the treatment of patients with rheumatoid arthritis (RA). MTX shows effects on disease activity and mortality. However, it is unclear whether the effect of MTX on mortality depends on its effect on disease activity.

Methods

In a post-hoc analysis we analysed the data of our cohort established in Ratingen, Germany, and included all patients starting treatment with MTX (n=271) between 1980 and 1987. One year after baseline (BL), response to MTX treatment was assessed using a modified ACR 20 response. Follow-up data of 250 patients were available after 10 and 18 years.

Results

After 1 year, there were 66% responders and 20% non-responders; only 14% had discontinued MTX treatment due to side effects or lack of efficacy. Most patients continued MTX treatment irrespective of efficacy. Ten years after BL, 61% of the patients were still treated with MTX. After 18 years, the responder-group showed a standardised mortality ratio of 1.6 compared to 3.2 for the group of non-responders. However, when adjusting for age, gender, response to MTX treatment one year after BL, number of swollen joints and comorbidities after 10 years an independent association of continued MTX treatment with lower mortality was found for the period 10 to 18 years after BL (hazard ratio (HR): 0.63, 95% confidence interval: 0.43–0.92, p=0.015).

Conclusion

In this cohort, the mortality lowering effect of continued MTX use was partly independent of its effect on disease activity. This finding may affect treatment decisions concerning RA patients with insufficient response to MTX.

Key words

rheumatoid arthritis, methotrexate, outcome measures, mortality, long-term follow-up

Dietmar Krause, MD
Bernadette Gabriel, MD
Gertraud Herborn, MD
Jürgen Braun, MD
Rolf Rau, MD, PhD

Please address correspondence and reprint requests to:
Dr Dietmar Krause,
Gerschermannweg 3,
D 45357 Essen, Germany.
E-mail: gundi.krause@t-online.de

Received on September 5, 2013; accepted in revised form on January 9, 2014.

Competing interests: none declared.

Introduction

In patients with rheumatoid arthritis (RA), mortality rates have been found increased in comparison to the general population. The first report on this issue had appeared in 1953 (1).

In many studies, predictors of premature death in RA patients are older age, male sex, lower socio-economic status, higher number of swollen joints, poor functional status and comorbidities (2, 3). Therapeutic interventions may improve survival rates in RA patients. Especially, treatment with methotrexate (MTX) has been associated with lower mortality rates of RA patients (4, 5). This effect seems likely to be linked with a positive effect of the drug on disease activity. As a possible consequence, MTX treatment may be stopped in case of insufficient clinical improvement, especially since toxicity of MTX is an issue of concern in some patients. However, the question of whether the observed impact of MTX on mortality rates of RA patients really depends on its clinical efficacy has not been addressed to date.

Since our group has data available of one of the oldest MTX cohorts in Europe, we were in a position to perform further analyses to shed some more light on this unresolved issue. At the Department of Rheumatology, Evangelisches Fachkrankenhaus Ratingen (Head Prof. R. Rau), between 1980 and 1987, all RA patients starting treatment with MTX (n=271) were enrolled in a prospective observational study. One year after baseline, response to MTX treatment was assessed, using a modification of the ACR 20 response criteria. Importantly, nearly all patients continued MTX treatment independent of their response. In 1995 (ten years after baseline) (5) and 2003 (18 years after baseline), the follow-up of 250 patients was available.

Materials and methods

Study population

All patients with definite or classic RA (6) who started MTX treatment in the Department of Rheumatology, Evangelisches Fachkrankenhaus Ratingen, Germany, between January 1, 1980 and December 31, 1987 were enrolled in a prospective observational study. Upon inclusion, all patients had active disease and all had failed to respond to at least one conventional disease-modifying anti-rheumatic drug (DMARD) other than MTX such as sulfasalazine. Leflunomide was not yet approved at this time point. Patients gave informed consent and all procedures were in accordance with the ethical standards of the Helsinki Declaration of 1975, as revised in 1983.

Treatment

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. This decision was made by the treating rheumatologist, there was no protocol to guide it. If needed, patients were allowed to continue treatment with non-steroidal anti-inflammatory drugs (NSAIDs) and/or corticosteroids. If the previous DMARD had been well tolerated and regarded as being at least somewhat effective, it was continued at full dosage together with MTX (5).

Clinical assessments

Standardised clinical evaluations were performed at baseline and every 1-3 months thereafter for the first year of MTX treatment. Response to treatment was evaluated one year after baseline.

The rates of improvement were graded as: ≥50% improvement, <50% and ≥20% improvement, and <20% improvement. In this analysis the groups with ≥50% improvement and with <50% and ≥20% improvement were combined as ≥20% improvement based on power calculations. Patients who discontinued MTX treatment within the first year made up a third group.

Improvement of ≥20% was defined as a ≥20% decrease in the swollen joint count (SJC) (32 joints were assessed: proximal interphalangeal and metacarpophalangeal joints, wrists, elbows, shoulders, knees, ankles, forefeet [counted as one joint each]) and the erythrocyte sedimentation rate (ESR). In addition, patient global assessment for disease activity had to be rated as mild or moderate on a four-point (absent, mild, moderate, severe) Likert scale. The dose of prednisone had to be ≤5mg/day. These response criteria are

comparable to those of the American College of Rheumatology (7) which had not yet been established at the initiation of this study.

In 1995/1996 (10 years after baseline) and again in 2003 (18 years after baseline), follow-up visits were performed - either at the outpatient clinic of Evangelisches Fachkrankenhaus Ratingen or at the patient's home. In all visits a complete physical examination including joint counts was performed, and the patients were asked to fill out the questionnaires. Comorbidities were classified using the Charlson score (8).

Statistical analysis

Standardised mortality ratios were calculated as the ratio of the observed number of deaths in specific age/sex bands of the patients in the study to the expected number of deaths in an age and sex matched sample of the general population of western Germany where nearly all patients came from (mortality charts of western Germany (9)), based on the number of person-years of follow-up.

Probability of survival was estimated as a function of time by the Kaplan-Meier method. The difference between groups was determined by the log-rank test. *p*-values less than 0.05 were considered significant.

For the whole observation period, the hazard ratios for death of patients with <20% MTX response were compared to those with ≥20% MTX response after adjusting for the baseline values of age, gender, rheumatoid factor (RF), SJC, and ESR. To estimate the effect of continued MTX use, further analyses were performed for the period between 10 - 18 years after baseline. In order to reduce bias caused by confounding by indication, we used a Cox model adjusting for age, gender, RF, response to MTX treatment one year after baseline, SJC 10 years after baseline, and whether or not MTX treatment was given 10 years after baseline. Serious adverse events (SAE) in the first 10 years of observation might have led to a continuously elevated risk of death (*e.g.* in case of lung fibrosis, liver cirrhosis or lymphoma) despite discontinuation of MTX treatment. This may bias the results and suggest a lower mortality in the MTX group. To largely exclude and diminish this bias, we repeated the analysis including only those patients who had not experienced any SAE.

For the statistical analysis we used SAS, version 9.2 (SAS Institute, Cary, NC).

Results

Patient characteristics

271 consecutive patients with definite RA were included into the study between January 1, 1980 and December 31, 1987. At baseline, their mean disease duration was 8.5 years, almost all patients (95%) had joint erosions, and the majority of patients were in a stage of rather advanced disease (63% in Steinbrocker stages III and IV). Patients had active disease, with a mean SJC of 18 (out of 32) and a mean ESR of 55 mm/hour. Almost all patients (96%) were treated with NSAIDs, 62% with prednisone (mean dosage of 4.5 mg/day). Nearly all patients rated their global disease activity as severe (Table I).

Treatment and response after one year

The mean MTX dosage was 17 mg/week (standard deviation: 4.4 mg/week), and 60% of patients switched from IV to oral administration (mostly 15 mg/week). In 79 cases (29.2%) MTX was given as monotherapy after discontinuation of the previous DMARD (10), while the remainder (70.8%) continued treatment with the DMARDs already taken before (*e.g.* parenteral gold, D-penicillamine or chloroquine) in addition to MTX (5).

Of those 250 (out of 271) patients who could be followed up to 18 years after baseline (92.3%), 165 patients (66%) had had a ≥20% response, and 50 patients (20%) had had a <20% response one year after baseline. In addition, 35 patients (14%) had discontinued MTX treatment due to lack of efficacy or due to side effects, mostly nausea, vomiting or stomatitis; MTX was continued in all other patients. Table I shows the demographic and clinical data at baseline of these 250 patients, as classified according to their response one year after baseline.

Table I. Demographic and clinical data at baseline.

Characteristic	≥20% improvement	<20% improvement	Discontinued treatment	Total
No. of patients	165	50	35	250
Mean age, years (SD)	56.2 (10.7)	58.7 (10.2)	62.7 (9.9)	57.5 (10.7)
Women, %	81.2	64.0	85.7	78.4
RF positive, %	86.6	94.0	80.0	87.1
Mean disease duration, years (SD)	8.3 (2.1)	8.6 (2.6)	8.8 (1.7)	8.4 (2.2)
Mean no. of previous DMARDs (SD)	1.7 (0.9)	2.1 (1.2)	2.0 (1.0)	1.8 (1.0)
Medication				
NSAIDs, %	95	98	100	96
Mean prednisone-equivalent, mg/day (SD)	4.5 (4.6)	4.1 (5.0)	5.0 (5.8)	4.7 (4.9)
Mean initial MTX dosage, mg (SD)	16.8 (4.5)	17.5 (4.6)	16.1 (3.9)	16.8 (4.4)
Measures of disease activity				
Mean patient's assessment of disease activity, 0-3 (SD)	2.85 (0.39)	2.76 (0.52)	2.77 (0.55)	2.82 (0.44)
Mean no. of swollen joints, 0-32 (SD)	18.6 (7.4)	15.1 (7.0)	17.4 (6.8)	17.7 (7.3)
Mean grip strength of both hands, kPa (SD)	45.0 (39.3)	44.1 (34.3)	36.7 (30.7)	43.6 (37.1)
Mean ESR, mm/h (SD)	55.3 (28.8)	59.1 (32.1)	65.5 (36.2)	57.7 (30.7)

RF: rheumatoid factor; DMARD: disease-modifying anti-rheumatic drug; NSAID: non-steroidal anti-inflammatory drug; MTX: methotrexate; ESR: erythrocyte sedimentation rate; SD: standard deviation.

Patient evaluation 10 and 18 years after baseline

The evaluation of the long term follow-up data successfully obtained in 250 out of 271 patients 10 years after baseline revealed that 88 patients (35.2%) had died. Another 59 patients (23.6%) died in the following 8 years. Thus, a total of 147 patients (58.8%) had died 18 years after baseline. Known causes of death were 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), septicaemia or infection (n=3, 1.2%) and atlanto-dental dislocation (n=1). The cause of death could not be determined in 43 patients (29.3%).

Out of the patients still alive 10 years after baseline (n=162), 99 (61.1%) were on MTX treatment. Eight years later, 103 patients were still living, 83 of which (80.6%) had been responders and 20 (19.4%) had been non-responders at year 1.

18 years after baseline, a significant difference between the response groups were found related to the mortality rates. The SMR in the group of MTX responders was 1.6 (95% confidence interval [CI]: 1.25–1.95) compared to 3.2 (95% CI: 2.16–4.14) in MTX non-responders (Table II).

Figure 1 shows the probability of survival for the patient groups with and without response after one year of MTX treatment. The difference is mainly generated during the first 10 years whereas the curves run fairly in parallel thereafter (p<0.001 by log rank test). In the Cox regression analysis, the hazard ratio for death was significantly higher in the patients not responding to MTX after adjustment for age, gender, rheumatoid factor positivity, number of swollen joints and ESR (Table III).

A Cox model adjusting for age, gender, RF positivity, response to MTX treatment after one year, number of swollen joints and comorbidities ten years after baseline as well as continuation of MTX treatment 10 years after baseline as covariates showed an independent effect of continued MTX treatment on mortality (hazard ratio [HR]: 0.63; 0.95 CI: 0.43-0.92, p=0.015), see Table IV.

This association of continued MTX treatment and lower mortality was not only seen in the whole cohort but also in the subgroup of non-responders. In this subgroup, the HR of death was 0.47 (0.95 CI: 0.15–1.43) for those patients who had been on MTX treatment 10 years after baseline. However, this was not significant due to small patient numbers in this group (n=23) (see Table V.)

Additional analyses were performed in patients who had not experienced SAEs in the first 10 years of MTX treatment. Among the patients still alive 10 years after baseline, 8 had experienced SAEs: multiple liver abscesses (n=1), lymphoma (n=2), liver cirrhosis (n=2), pneumonitis (n=1), lung fibrosis (n=1), and seizures (n=1). These 8 patients were excluded from further analyses.

In the group of patients without SAEs, the HR for death was 0.61 (0.95 CI: 0.41–0.90) for patients continuing MTX treatment 10 years after baseline. In the subgroup of non-responders, the HR was 0.47 (0.95 CI: 0.14–1.61).

Table II. Mortality data of the entire observation period.

	≥20% improvement	<20% improvement
No. of patients	165	50
No. of deceased patients (%)	82 (49.7)	39 (78.0)
Standardised mortality ratio (95% confidence interval)	1.6 (1.25–1.95)	3.2 (2.16–4.14)

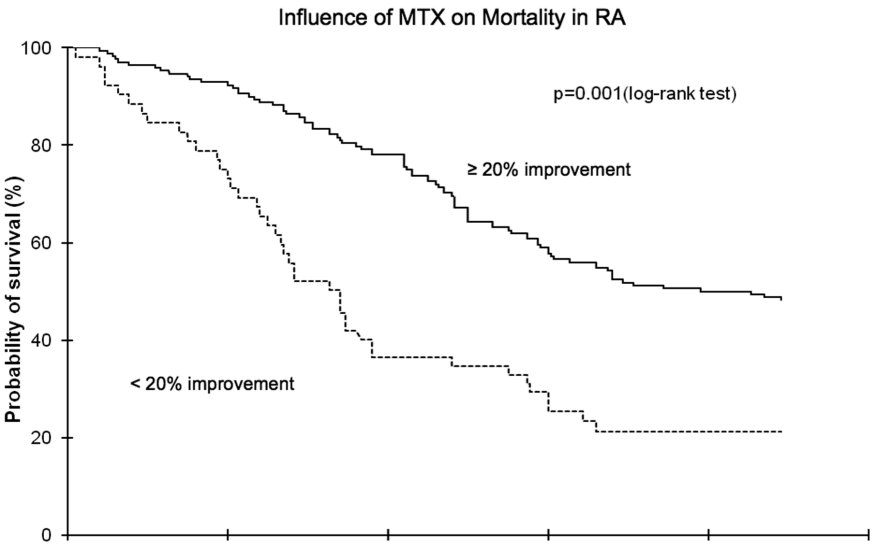

Fig. 1. Probability of survival of patients with and without 20% improvement after the first year of methotrexate treatment.

Table III. Predictors of all-cause mortality for the entire observation period.

Variable	Hazard ratio	95% confidence interval	Chi-square	p-value
No improvement ≥20% after the first year of MTX treatment	1.89	1.35–2.67	13.5	0.0002
Age	1.08	1.06–1.10	80	<0.0001
Female gender	0.66	0.46–0.93	5.66	0.017
RF positivity	0.97	0.63–1.50	0.02	0.88
No. of swollen joints at baseline (0–32)	1.01	0.99–1.03	0.45	0.50
ESR at baseline	1.00	0.99–1.01	0.0004	0.98

RF: rheumatoid factor; MTX: methotrexate; ESR: erythrocyte sedimentation rate.

Discussion

In this post-hoc analysis of a prospec-

Table IV. Predictors of all-cause mortality for the period 10–18 years after baseline.

Variable	Hazard ratio	95% confidence interval	Chi-square	*p*-value
Age	1.07	1.05–1.10	40.4	<0.0001
Female gender	0.67	0.43–1.04	3.23	0.072
RF positivity	0.91	0.61–1.75	0.013	0.91
No improvement of ≥20% after the first year of MTX treatment	1.64	1.02–2.64	4.11	0.043
No. of swollen joints 10 years after baseline (0–32)	1.01	1.00–1.03	2.04	0.15
Comorbidity 10 years after baseline	1.02	0.72-1.45	0.014	0.91
Continuation of MTX treatment (10 years after baseline)	0.63	0.43 – 0.92	5.88	0.015

RF: rheumatoid factor; MTX: methotrexate.

Table V. Predictors of all-cause mortality of non-responders for the period 10–18 years after baseline.

Variable	Hazard ratio	95%confidence interval	Chi-square	*p*-value
Age	1.11	1.02–1.20	6.05	0.014
Female gender	1.03	0.30–3.48	0.002	0.97
RF positivity	0.68	0.05–8.47	0.013	0.76
No. of swollen joints 10 years after baseline (0–32)	0.99	0.93–1.05	0.19	0.66
Comorbidity 10 years after baseline	4.13	0.98-17.40	3.74	0.053
Continuation of MTX treatment (10 years after baseline)	0.47	0.15 – 1.43	1.77	0.18

RF: rheumatoid factor; MTX: methotrexate.

tive observational one centre trial that started in the early eighties, the long term mortality of RA patients after initiation of MTX treatment could be evaluated. The data show differences in the mortality rates of responders and non-responders to MTX therapy but they also suggest that continuation of MTX therapy rather decreased mortality.

About 33 year ago, MTX was not approved for the treatment of RA in Germany due to lack of placebo-controlled studies at that time. The first placebo-controlled trial was actually published not before 1984 (11). Therefore, only patients with severe disease were treated with MTX in our country. Indeed, all patients in this study had very active disease at baseline as shown by the number of swollen joints and the high ESR values. Of interest, MTX was started in relatively high dosages which would nowadays be considered optimal (12) and which have been recently recommended by EULAR (13).

After a follow-up of 18 years, 59% of the patients had died. This corresponds to an SMR of 2.0. This is comparable to other long-term RA cohorts. In a recent review a mean SMR of 1.74 was calculated using data of 19 clinic based non-inception cohorts (3). For the largest cohort with 3501 patients who had been followed up for a mean of 35 years in the ARAMIS registry, an SMR of 2.26 was reported (14). In a study performed in the U.K. with 489 RA patients who had been followed up for 18 years, an SMR of 2.5 was calculated. In this study, age, sex and disease duration were identified as prognostic factors for mortality (15). Of interest, the SMR decreased from 3.0 (16) after a mean of 11 years to 2.5 after 18 years and raised again to 2.7 after 21.5 years (17). These data are largely comparable to our cohort with an SMR of 2.6 after 10 (5) and 2.0 after 18 years. Thus, the SMR seems to vary in the long-term follow-ups of RA cohorts showing an excess mortality emerging only 10 years after disease onset (18). Due to convincing therapeutic successes in the era of biologics, SMRs may have been decreasing in RA over the last decades (19). The reason for an increased mortality in RA is primarily thought of as accelerated atherosclerosis, with cardiovascular disease as the acute cause of premature death in more than 50% of patients (20). Compared to the general population, the rate of infection as cause of death in RA, being >14%, is 3fold elevated (3).

There are non-modifiable and modifiable predictors of mortality in RA (21). Age and sex are typical non-modifiable predictors. In our cohort, older age and male gender proved to be statistically significant predictors of mortality (Table III). This is in accordance with data from other cohorts (3).

Joint counts, traditional clinical measures of disease activity in RA, have been identified as modifiable predictors of mortality in only 50% of RA cohorts (3). In our trial, there was no effect of the baseline SJC or of ESR on mortality rates nor was there any impact of the SJC 10 years after baseline on the mortality rates in the ensuing 8 years. This is different from the findings of a recent study (22), but is in accordance with several other studies (23-24).

In our cohort, we found an association of response to MTX treatment one year after baseline with survival rates during the following 17 years. As shown in Fig. 1, this association is distinct during the first 10 years of observation. Nonetheless, it remained significant for the whole observation period with a hazard ratio (HR) of 1.89 (0.95 CI: 1.35–2.67) (Table III).

The HR of mortality in patients with continued MTX use 10 years after baseline was 0.63 (0.95 CI: 0.43 – 0.92) during the next 8 years (Table IV), compared to discontinuation of MTX. This is in accordance with the important study of Choi *et al*. who reported a mortality HR for MTX use of 0.4, compared to no MTX use (4). In a time-varying multivariate Cox regression model that included propensity score adjustments, Wasko *et al*. found an association of MTX use with a reduction in mortality of even 70% (25).

This suggests that continued MTX use reduces the risk of cardiovascular events, since the majority of deaths were caused by cardiovascular diseases. Because of a lack of an association between MTX use and traditional cardiovascular risk factors such as lipid pro-

files or insulin resistance (26), it seems likely that MTX reduces cardiovascular risk through its anti-inflammatory properties (27). Whether this reduced risk is the result of the reduction in systemic inflammation in general or due to direct effects on atherosclerotic lesions is unclear (26).

In our study, the association of long-term MTX use with a decreased risk of mortality was clearly seen, even after adjusting for the response to MTX treatment one year after baseline (Table IV). Thus, the effect of MTX on survival seems to be partly independent of the efficacy of the drug on systemic inflammation. Even in the group of non-responders, the HR for death was reduced to 0.47 for the patients continuing MTX treatment over 10 years, compared to those who had stopped MTX treatment (Table V). However, this finding was no longer statistically significant due to the small number of patients in this group (0.95 CI: 0.15–1.43).

In order to remove confounding effects of SAEs that might have biased the result in favour of a lower mortality in the MTX group, we undertook a second analysis after exclusion of patients with SAEs. It could be shown that in the group of patients without SAE, the HR for death remained low for those who used MTX continuously.

The strength of this study is the high percentage of patients who continued MTX use, even after a minor response to MTX after the first year of treatment. This treatment strategy had resulted from a lack of other efficacious DMARDs in the early eighties.

However, due to the observational character of this study, the results may rather be considered hypothesis generating than providing final proof of an important clinically relevant concept. In non-randomised studies and in all long-term observational trials describing mortality outcomes, confounding by indication cannot be ruled out. Another weakness of this study is the relatively small number of patients which seems to be the main reason for the statistically insignificant results in the group of MTX non-responders. The fact that most patients in this study had rather advanced disease at baseline may limit the relevance of our results for patients treated according to the treat-to-target approach who may never get to the late disease stage that many of our patients were in when entering the study.

However, taken together, the results of this study strongly suggest that the mortality lowering effect of long-term MTX use may be present even in patients not showing clinical improvement of ≥20% after one year of treatment. This effect may be less pronounced in patients with a lower mortality risk – for example due to modern treatment strategies.

In conclusion, the results of this study are consistent with the assumption that continued MTX use in patients with severe RA is associated with a decline in mortality rates. This effect seems to be partly independent of the clinical MTX response. This finding may have an impact on treatment decisions concerning RA patients with a minor response to MTX treatment, favouring add-on therapy over switching to other DMARDs.

References

1. COBB S, ANDERSON F, BAUER W: Length of life and cause of death in rheumatoid arthritis. *N Engl J Med* 1953; 249: 553-6.
2. WOLFE F, MICHAUD K, GEFELLER O, CHOI HK: Predicting mortality in patients with rheumatoid arthritis. *Arthritis Rheum* 2003; 48: 1530-42.
3. SOKKA T, ABELSON B, PINCUS T: Mortality in rheumatoid arthritis: 2008 update. *Clin Exp Rheumatol* 2008; 26 (Suppl. 51): 35-61.
4. CHOI HK, HERNÁN MA, SEEGER JD, ROBINS JM, WOLFE F: Methotrexate and mortality in patients with rheumatoid arthritis: a prospective study. *Lancet* 2002; 359: 1173-7.
5. KRAUSE D, SCHLEUSSER B, HERBORN W, RAU R: Response to methotrexate is associated with reduced mortality in patients with severe rheumatoid arthritis. *Arthritis Rheum* 2000; 43: 14-21.
6. ROPES MW, BENNETT GA, COBB S, JACOX RF, JESSAR RA: 1958 revision of diagnostic criteria for rheumatoid arthritis. *Bull Rheum Dis* 1995; 9: 175-6.
7. FELSON DT, ANDERSON JJ, BOERS M *et al*.: American College of Rheumatology preliminary definition of improvement in rheumatoid arthritis. *Arthritis Rheum* 1995; 38: 727-35.
8. CHARLSON ME, POMPEI P, ALES KL, MAC KENZIE CR: A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987; 40: 373-83.
9. STATISTICAL YEARBOOK 2003 FOR THE FEDERAL REPUBLIC OF GERMANY: Federal Statistical Office, Wiesbaden, 2003.
10. YAZICI Y: Treat-to-target: measures. *Clin Exp Rheumatol* 2012; 30 (Suppl. 73): S7-S9.
11. COURY FF, WEINBLATT ME: Clinical trials to establish methotrexate as a therapy for rheumatoid arthritis. *Clin Exp Rheumatol* 2010; 28 (Suppl. 61): 9-12.
12. VISSER K, VAN DER HEIJDE D: Optimal dosage and route of administration of methotrexate in rheumatoid arthritis: a systematic review of the literature. *Ann Rheum Dis* 2009; 68: 1094-9.
13. SMOLEN JS, LANDEWÉ R, BREEDVELD FC *et al*.: EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs. *Ann Rheum Dis* 2010; 69: 964-75.
14. WOLFE F, MITCHELL DM, SIBLEY JT *et al*.: The Mortality of rheumatoid arthritis. *Arthritis Rheum* 1994; 37: 481-94.
15. SYMMONS DP, PRIOR P, SCOTT DL, BROWN R, HOWKINS CF: Factors influencing mortality in rheumatoid arthritis. *J Chronic Dis* 1986; 39: 137-45.
16. PRIOR P, SYMMONS DP, SCOTT DL, BROWN R, HAWKINS CF: Cause of death in rheumatoid arthritis. *Br J Rheumatol* 1984; 23: 92-9.
17. SYMMONS DP, JONES MA, SCOTT DL, PRIOR P: Longterm mortality outcome in patients with rheumatoid arthritis: Early presenters continue to do well. *J Rheumatol* 1998; 25: 1072-7.
18. RADOVITS BJ, FRANSEN J, AL SHAMMA S, EIJSBOUTS AM, VAN RIEL PLCM, LAAN RFJM: Excess mortality emerges after 10 years in an inception cohort of early rheumatoid arthritis. *Arthritis Care Res* 2010; 62: 363-70.
19. BJORNADAL l, BAECKLUNG E, YIN L, GRANATH F, KLARESKOG L, EBKOMA A: Decreasing mortality in patients with rheumatoid arthritis: result from a large population based cohort in Sweden, 1964-95. *J Rheumatol* 2002; 29: 906-12.
20. SYMMONS DP, GABRIEL SE: Epidemiology of CVD in rheumatic disease, with focus on RA and SLE. *Nat Rev Rheumatol* 2011; 7: 399-408.
21. PINCUS T, CASTEJON I, BERGMAN MJ, YAZICI Y: Treat-to-target; not as simple as it appears. *Clin Exp Rheumatol* 2012; 30 (Suppl. 73): S10-20.
22. LISTING J, KEKOW, J, MANGER B *et al*.: Mortality in rheumatoid arthritis: the impact of disease activity, treatment with glucocorticoids, TNF-α inhibitors and rituximab. *Ann Rheum Dis* Nov 29 2013 [Epub ahead of print].
23. KREMER JM: Safety, efficacy, and mortality in a long-term cohort of patients with rheumatoid arthritis taking methotrexate: followup after a mean of 13.3 years. *Arthritis Rheum* 1997; 40: 984-5.
24. CHEHATA JC, HASSELL AB, CLARKE SA *et al*.: Mortality in rheumatoid arthritis: relationship to single and composite measure of disease activity. *Rheumatology* 2001; 40: 447-52.
25. WASKO MCM, DASGUPTA A, HUBERT H, FRIES JF, WARD MM: Propensity-adjusted association of methotrexate with overall survival in rheumatoid arthritis. *Arthrits Rheum* 2013; 65: 334-42.
26. WESTLAKE SL, COLEBATCH AN, BAIRD J *et al*.: The effect of methotrexate on cardiovascular disease in patients with rheumatoid arthritis: a systematic literature review. *Rheumatology* 2010; 49: 295-307.
27. MICHA R, IMAMURA F, WYLER VON BALLMOOS M *et al*.: Systematic review and meta-analysis of methotrexate use and risk of cardiovascular disease. *Am J Cardiol* 2011; 108: 1362-70.