Long-term treatment response in rheumatoid arthritis patients starting adalimumab or etanercept with or without concomitant methotrexate

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Abstract

Objective

To observe long-term clinical response and drug survival in a prospective two-year cohort study in rheumatoid arthritis (RA) patients starting adalimumab or etanercept treatment, with or without methotrexate (MTX), after failure of conventional DMARD therapy, including MTX.

Methods

Disease activity score of 28 joints (DAS28) and Health Assessment Questionnaire (HAQ) were collected of 873 consecutive RA patients, treated with adalimumab or etanercept, prospectively at baseline, 4, 16, 28, 40, 52, 78 and 104 weeks of biological therapy. Sustained minimal disease activity (MDA), DAS28 <2.6 for at least 24 consecutive weeks, biological discontinuation, ΔHAQ and ΔDAS28 were compared between patients treated with or without concomitant MTX for etanercept and adalimumab separately.

Results

More patients treated with adalimumab and MTX (42%) achieved sustained MDA than patients without MTX (18%). The hazard ratio (HR) was 2.3 [1.4-3.9]. No significant difference was found in etanercept treatment (with MTX 33% vs. 28% without MTX), HR 1.1 [0.8-1.6]. More patients treated without MTX discontinued treatment than patients with MTX co-treatment in adalimumab (HR 2.1 [1.5-3.0]) and etanercept (HR 1.9 [1.0-3.4]). The mean decrease in DAS28 over time was higher for patients treated with MTX in adalimumab (regression coefficient (RC): 0.57, p<0.001), but was not significantly different in etanercept treatment (RC 0.05, p=0.427). No significant differences were found in ΔHAQ.

Conclusion

Treatment discontinuation is lower in patients treated with MTX in both adalimumab and etanercept treatment. However, considering good clinical response, in contrast to etanercept, a synergetic effect of MTX is observed only in adalimumab treatment.

Key words

rheumatoid arthritis, cohort studies, methotrexate, tumour necrosis factor-alpha

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Introduction

Rheumatoid arthritis (RA) is a progressive systemic inflammatory disorder affecting joints. Treatment commonly starts with non-steroidal anti-inflammatory drugs (NSAIDs) and disease modifying anti-rheumatic drugs (DMARDs), preferably methotrexate (MTX) (1). A biological agent, like tumour necrosis factor (TNF) blockers adalimumab or etanercept, is added when DMARD therapy is not effective or not tolerated in sufficient dose (1) and showed their effectiveness in treatment of RA (2).

Apart from its anti-inflammatory mechanism, MTX also reduces immunogenicity in adalimumab treated patients (3). Anti-adalimumab antibodies are less frequently detected in patients treated with a combination of adalimumab and MTX compared to treatment without concomitant MTX. Low amounts of detectable anti-adalimumab antibodies are associated with a higher adalimumab drug level in patients receiving combination therapy (3). Moreover, a higher adalimumab drug level is associated with good clinical response (3-5). The role of immunogenicity in etanercept is not yet clear. In some studies no anti-etanercept antibodies are detected, whereas others reported antibodies in low quantities (6, 7). However, the clinical relevance of these anti-etanercept antibodies has not yet been proven. The difference in immunogenicity could result in a different effect of MTX in etanercept and adalimumab treatment.

Therapy with etanercept or adalimumab combined with MTX is more effective than MTX alone (8-10). Some patients, however, are intolerant for MTX and start biological therapy without MTX. A few studies showed a preference for combining adalimumab or etanercept with MTX instead of no MTX (10-14). However, different study populations were used. Some studies included MTX naïve patients and others included patients who failed MTX before start of a biological agent. Both outcomes should be interpreted differently, in which the latter study population correspond more to daily clinical practice.

Furthermore, the additional long-term effect of MTX in adalimumab and etanercept treatment is still unclear in patients with ongoing disease activity despite MTX use. Therefore, the aim of the study is to observe clinical response and drug survival in a prospective two-year cohort study in rheumatoid arthritis patients starting adalimumab or etanercept with or without concomitant MTX after failure on DMARD therapy, including MTX.

Materials and methods

Study subjects

Patients with RA participated in an observational prospective cohort study at the Amsterdam Rheumatology and Immunology Centre, Reade, of which 507 patients were included in the adalimumab cohort and 541 in the etanercept cohort. A part of these patients were analysed previously (5, 15). The adalimumab cohort started in February 2004 and the etanercept cohort in December 2004 and are still ongoing cohorts. For this study, adalimumab treated patients were included till January 2013 and etanercept treatment till November 2012. Treatment allocation was at the discretion of the patients' own treating rheumatologist and the inclusion criteria for these cohorts were: RA according to the American College of Rheumatology criteria of 1987 (16) or based on the expert opinion of the treating rheumatologist. To receive a biological agent, treatment with at least 2 DMARDs, including MTX, should have failed. If patients consecutively received both etanercept and adalimumab, only data regarding the first TNF-inhibitor was analysed. Patients were excluded for further analyses if no data was available about MTX use at baseline. Patients received their TNF-inhibitor treatment as monotherapy or in combination with concomitant DMARD therapy or prednisone. All patients treated with adalimumab received 40 mg subcutaneously every other week and patients treated with etanercept received 50 mg subcutaneously weekly or 25 mg subcutaneously twice a week.

In each TNF-inhibitor therapy, two subgroups were distinguished based on concomitant MTX use at the start of the biological treatment: TNF-

inhibitor with concomitant MTX and TNF-inhibitor without concomitant MTX. Other DMARD co-therapy was allowed in both subgroups and could be changed during the follow-up of the study. Discontinuation of biologic treatment was a decision of the treating rheumatologist, in which treatment failure was not specified explicitly. All patients gave written informed consent and the study was approved by the local medical ethics committee.

Clinical measurements

Disease activity was assessed using the 28-joint disease activity score (DAS28), at baseline and 4, 16, 28, 40, 52, 78 and 104 weeks thereafter. Achieving sustained minimal disease activity (MDA) during 2 years of follow-up was defined as DAS28 below 2.6 for at least 24 weeks. Functional ability was measured with the Health Assessment Questionnaire (HAQ) at the same time points as the DAS28. Improvement in HAQ and DAS28 were described at each visit compared to baseline. Finally, biological treatment discontinuation was measured during the 2-year follow-up.

Table I. Demographics and baseline characteristics for adalimumab*.

	All adalimumab (n=420)	With MTX (n=330)	Without MTX (n=90)
Demographics			
Age, mean ± SD years	53.7 ± 12.4	53.2 ± 12.1	55.4 ± 13.3
Female, no. (%)	338 (81)	265 (80)	73 (81)
BMI, median (IQR) years	25.2 (22.1-29.3)	25.1 (22.0-29.0)	25.2 (22.3-30.1)
Prior DMARD			
Prior DMARDs use, median (IQR), no.	3 (2-3)	3 (2-3)	3 (2-4)†
Prior Biologicals use, no. (%)	87 (21)	62 (19)	25 (28)
MTX use, no. (%)	330 (79)	330 (100)	0
MTX dosage, median (IQR) mg/week	25 (15-25)	25 (15-25)	NA
Other DMARD use, no. (%)	141 (34)	110 (33)	31 (34)
Prednisone use, no. (%)	129 (31)	95 (29)	34 (38)
Prednisone dosage, median (IQR) mg/day	7.5 (5.0-10.0)	7.5 (5.0-10.0)	10.0 (5.0-15.0)†
Disease status			
Disease duration, median (IQR) years	7 (3-16)	7 (2-15)	9 (4-19)†
IgM-RF positive, no. (%)	287 (68)	220 (67)	66 (73)
Erosive disease, no. (%)	258 (61)	194 (59)	63 (70)
ACPA positive, no. (%)	283 (67)	223 (68)	59 (66)
DAS28, mean ± SD	4.9 ± 1.4	4.7 ± 1.3	5.3 ± 1.3†
ESR, median (IQR) mm/hour	22 (10-41)	20 (9-36)	30 (12-56)†
CRP, median (IQR) mg/l	10 (4-23)	10 (3-21)	15 (5-29)†
HAQ, mean ± SD	1.23 ± 0.70	1.17 ± 0.66	1.45 ± 0.78†

*MTX: methotrexate; SD: standard deviation; BMI: body mass index; IQR: interquartile range; DMARDs: disease-modifying anti-rheumatic drugs; IgM-RF: IgM rheumatoid factor; ACPA: anti-citrullinated protein antibody; DAS28: 28-joint disease activity score; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; HAQ: health assessment questionnaire, NA: not applicable.
†There is a significant difference between the groups with and without MTX for prior DMARD use (p=0.001), prednisone dosage (p=0.018), disease duration (p=0.042), ESR (p=0.001), CRP (p=0.021), HAQ (p=0.006).

Statistical analysis

Patients receiving adalimumab or etanercept treatment were analysed separately. Baseline characteristics were compared between patients treated with concomitant MTX and patients treated without concomitant MTX using an independent sample t-test, Mann-Whitney U-test or chi-square test depending on the normal distribution of each baseline characteristic. To investigate sustained MDA rate and discontinuation rate after 2 years of follow-up, a chi-square test was used. Cox regression analyses were used to estimate hazard ratio (HR) for sustained MDA and drug survival.

The changes in DAS28 and HAQ over time were analysed using longitudinal analyses. Because of missing data in a cohort study design, linear mixed model with a random intercept was chosen. HR were adjusted for confounders; sex, disease duration and DAS28 at baseline. The change in DAS28 and HAQ was adjusted for sex, age and respectively baseline DAS28 or HAQ. No imputation methods were used, resulting in a responder analyses for ΔDAS28 and ΔHAQ. *P*-values less than 0.05 (2-sided) were considered significant. For all analyses, SPSS for Windows v. 21.0 was used.

Results

Baseline characteristics

Four hundred and twenty patients were treated with adalimumab and 453 patients with etanercept. The proportion of patients treated with concomitant MTX *versus* without was 3.7:1 for adalimumab (n=330 with MTX, n=90 without MTX) and 2.1:1 for etanercept (n=308 with MTX, n=145 without MTX). Baseline characteristics for adalimumab are shown in Table I and for etanercept in Table II. In the adalimumab group, 49% of patients (n=211) completed 2 years of follow-up (with MTX 54% [n=178], without MTX 37% [n=33]) and 51% of patients (n=234) in the etanercept group (with MTX 57% [n=176], without MTX 40% (n=58)). The reasons for incomplete follow-up or treatment discontinuation before 2 years of follow-up, or biologic treatment duration less than 2 years. The median duration of adalimumab treatment was 78 weeks [28–104] and 104 weeks [28–104] for etanercept treatment. Significant differences were found at baseline in the adalimumab group between patients treated with and without concomitant MTX; respectively for prior DMARD use (including MTX use) (median n=3 [2-3] *vs*. n=3 [2–4]; p=0.001), prednisone dosage (median 7.5 mg/day [5.0–10.0] *vs*. 10.0 mg/day [5.0–15.0]; p=0.018), disease duration (median 7 years [3–15] *vs*. 9 years [4–19]; p=0.042), DAS28 (mean 4.7±1.3 *vs*. 5.3±1.3; p=0.001), erythrocyte sedimentation rate (ESR) (median 20 mm/h [9-36] *vs*. 30 mm/h [12–56]; p=0.001), CRP (median 10 mg/l [3–21] *vs*. 15 mg/l [5–29]; p=0.021) and HAQ (mean 1.169±0.663 *vs*. 1.446±0.776; p=0.006).

Within the etanercept group, only ESR was significantly lower in patients treated with concomitant MTX com-

Table II. Demographics and baseline characteristics for etanercept*.

	All etanercept (n=453)	With MTX (n=308)	Without MTX (n=145)
Demographics			
Age, mean ± SD years	53.6 ± 13.1	53.0 ± 12.9	54.8 ± 13.6
Female, no. (%)	358 (79)	241 (78)	118 (81)
BMI, median (IQR) years	24.8 22.0-29.1)	24.8 (22.1-29.1)	24.8 (21.7-29.5)
Prior DMARD			
Prior DMARDs use, median (IQR), no.	2 (2-3)	2 (2-3)	3 (2-4)
Prior Biologicals use, no. (%)	80 (18)	53 (17)	27 (19)
MTX use, no. (%)	308 (68)	308 (100)	0
MTX dosage, median (IQR) mg/week	25 (15-25)	25 (15-25)	NA
Other DMARD use, no. (%)	149 (33)	101 (33)	48 (33)
Prednisone use, no. (%)	147 (33)	99 (32)	48 (33)
Prednisone dosage, median (IQR) mg/day	7.5 (5.0-10.0)	7.5 (5.0-10.0)	7.5 (5.0-10.0)
Disease status			
Disease duration, median (IQR) years	6 (2-15)	7 (2-15)	5 (2-16)
IgM-RF positive, no. (%)	312 (69)	213 (69)	99 (68)
Erosive disease, no. (%)	272 (60)	192 (62)	80 (55)
ACPA positive, no. (%)	292 (65)	198 (64)	94 (65)
DAS28, mean ± SD	5.0 ± 1.3	4.9 ± 1.3	5.0 ± 1.3
ESR, median (IQR) mm/hour	20 (10-38)	19 (10-37)	22 (11-42)†
CRP, median (IQR) mg/l	7 (3-17)	7 (3-16)	7 (4-20)
HAQ, mean ± SD	1.29 ± 0.68	1.25 ± 0.68	1.38 ± 0.68

*MTX: methotrexate; SD: standard deviation; BMI: body mass index; IQR: interquartile range; DMARDs: disease-modifying anti-rheumatic drugs; IgM-RF: IgM rheumatoid factor; ACPA: anti-citrullinated protein antibody; DAS28: 28-joints disease activity score; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; HAQ: health assessment questionnaire; NA: not applicable.
†There is a significant difference between the groups with and without MTX for ESR (p=0.046).

pared to no MTX co-treatment (median 19 mm/h [10-37] *vs*. 22 mm/h [11–42]; p=0.046).

Sustained minimal disease activity

Significantly more patients treated with adalimumab and concomitant MTX achieved sustained MDA than patients treated with adalimumab without concomitant MTX (respectively 42% [n=131] *vs*. 18% [n=16]; p<0.001). In the etanercept group, no significant difference was found in achieving sustained MDA (with MTX 33% [n=102] *vs*. without MTX 28% [n=40]; p=0.237).

Following a cox regression analysis, hazard ratio (HR) to achieve sustained MDA in adalimumab treatment was 2.3 (Confidence Interval (CI) 95% [1.4–3.9]; p=0.001) for patients treated with MTX *vs*. without MTX. After adjusting for baseline characteristics, as is described in the method section, sex, disease duration and DAS28, HR was 2.0 (CI 95% [1.2–3.4]; p=0.012). In the etanercept treatment group, the hazard ratio for achieving sustained MDA was 1.1 for patients treated with concomitant MTX, compared to patients without MTX (CI 95% [0.8–1.6], p=0.535). The adjusted HR was 1.1 (CI 95% [0.7–1.5]; p=0.763). Data is shown in Table III and the survival data is shown in Figure 1.

Treatment discontinuation

As is shown in Table III, 153 patients discontinued adalimumab treatment due to failure (n=85), adverse events (n=45), remission (n=3), other reasons (n=17) or reason of discontinuation was missing (n=3). For etanercept, 178 patients discontinued treatment: 101 patients due to failure, 42 due to adverse events, 3 because of death, 31 because of other reasons and for 1 patients reason of discontinuation was missing. More patients treated without concomitant MTX discontinued adalimumab treatment than patients with MTX (respectively 56% [n=50] *vs*. 31% [n=103]; p<0.001). Moreover, more etanercept treated patients without MTX discontinued treatment than patients with concomitant MTX (respectively 48% [n=69] *vs*. 35% [n=109]; p=0.015). Following cox regression analysis, HR was 2.1 (CI 95% [1.5–3.0]; p<0.001) for adalimumab treated patients with MTX *vs*. without MTX co-treatment. The adjusted HR was 2.2 (CI 95% [1.5–3.0], p<0.001). For etanercept, HR was 1.5 (CI 95% [1.1–2.0]; p=0.010) for patients treated with MTX *vs*. without MTX co-treatment (adjusted HR 1.5 (CI 95% [1.1–2.0]; p=0.020)). The survival data is shown in Figure 1 and Table III.

ΔDAS28 and ΔHAQ

Following the responder analysis, the development of DAS28 and HAQ over time is shown in Figure 2. The average decrease in DAS28 over time was, unadjusted, 0.36 points higher for patients treated with adalimumab and concomitant MTX compared to no concomitant MTX use (p<0.001). The adjusted regression coefficient (RC) was 0.57 (p<0.001). Patients treated with etanercept and concomitant MTX did not significantly differ in ΔDAS28 from patients using no concomitant MTX (unadjusted RC 0.12, p=0.066; adjusted RC 0.05, p=0.427). Due to the missing data in HAQ, only data at baseline, 16, 52, 78 and 104 weeks thereafter were used for analysis. As is shown in Table III, no significant differences were found in ΔHAQ in both adalimumab (unadjusted RC -0.15, p=0.124, adjusted RC -0.09, p=0.320) and etanercept (unadjusted RC 0.01, p=0.764, adjusted RC 0.04, p=0.365) treated patients.

Because the sharpest decline in DAS28 was seen in the first 16 weeks, additional analyses were done in which the data was split in the first 16 weeks and thereafter. The difference between the subgroups in adalimumab treatment was the strongest in the first 16 weeks, but was also significant in the weeks thereafter (data not shown). In etanercept, no differences were seen when the data was split before and after 16 weeks of treatment.

Discussion

This 2-year follow-up observational study of 873 RA patients showed that patients treated with adalimumab and concomitant MTX were more likely to achieve sustained minimal disease activity (MDA) compared to no conco-

Table III. Clinical response and drug survival.

	With MTX	Without MTX	*p*-value
Adalimumab			
No. of patients (%)	330 (79)	90 (21)	
MDA rate, no. (%)	131 (42)	16 (18)	<0.001
Unadjusted HR (95% CI)	2.3 (1.4-3.9)	Reference	0.001
Adjusted HR (95% CI)*	2.0 (1.2-3.4)	Reference	0.012
Discontinuation rate, no. (%)	103 (31)	50 (56)	<0.001
Unadjusted HR (95% CI)	Reference	2.1 (1.5-3.0)	<0.001
Adjusted HR (95% CI)*	Reference	2.2 (1.5-3.0)	<0.001
Reasons for discontinuation, no. (%)			
Inefficacy	51 (50)	34 (68)	<0.001
Adverse events	34 (33)	11 (22)	0.621
Other	15 (15)	5 (10)	0.690
Delta DAS28			
Unadjusted RC (95% CI)	0.36 (0.20-0.51)	Reference	<0.001
Adjusted RC (95% CI)**	0.57 (0.43-0.71)	Reference	<0.001
Delta HAQ			
Unadjusted RC (95% CI)	-0.15 (-0.34-0.04)	Reference	0.124
Adjusted RC (95% CI)**	-0.09 (-0.27-0.09)	Reference	0.320
Etanercept			
No. of patients (%)	308 (68)	145 (32)	
MDA rate, no. (%)	102 (33)	40 (28)	0.237
Unadjusted HR (95% CI)	1.1 (0.8-1.6)	Reference	0.534
Adjusted HR (95% CI)*	1.1 (0.7-1.5)	Reference	
Discontinuation rate, no. (%)	110 (35)	69 (48)	0.013
Unadjusted HR (95% CI)	Reference	1.5 (1.1-2.0)	0.010
Adjusted HR (95% CI)*	Reference	1.5 (1.1-2.0)	0.020
Reasons for discontinuation, no. (%)			
Inefficacy	59 (54)	42 (61)	0.016
Adverse events	28 (26)	14 (20)	0.820
Other	21 (19)	11 (16)	0.759
Delta DAS28			
Unadjusted RC (95% CI)	0.12 (-0.01-0.25)	Reference	0.066
Adjusted RC (95% CI)**	0.05 (-0.08-0.18)	Reference	0.427
Delta HAQ			
Unadjusted RC (95% CI)	0.01 (-0.08-0.11)	Reference	0.764
Adjusted RC (95% CI)**	0.04 (-0.05-0.12)	Reference	0.365

*Hazard ratios were adjusted for sex, disease duration, 28-joint disease activity score (DAS28).
**Regression coefficients for DAS28 were in both adalimumab and etanercept treatment adjusted for sex, age and baseline DAS28. The regression coefficient of the Health Assessment Questionnaire (HAQ) was adjusted for: age, sex and baseline HAQ.
MTX: methotrexate; MDA: minimal disease activity; HR: hazard ratio; RC: regression coefficient; CI: confidence interval.

mitant MTX. Moreover, fewer patients discontinued treatment prematurely when concomitant MTX was used. This was observed for both adalimumab and etanercept treatment. The improvement in DAS28 was significantly better for adalimumab patients using concomitant MTX instead of no MTX.

In our study, patients respond insufficiently to MTX or did not tolerate effective MTX dose before start of biological treatment. Although insufficient, MTX affect disease activity and inflammation at the start of the biological, but no additional effect of MTX on disease activity is expected. Therefore, a different treatment response between patients treated with and without concomitant MTX could define a synergetic effect of MTX on biological treatment.

For etanercept treatment, we found no significant difference between patients receiving concomitant MTX and no MTX in achieving sustained MDA. This is in contrast to previous studies which showed a benefit for concomitant MTX in etanercept treatment (10, 12, 13). Patients included in the TEMPO study (RCT) had a MTX-free time for at least 6 months before the start of the study (10). Therefore it is reasonable that etanercept and MTX together affected disease status more than etanercept- or MTX-monotherapy would do. Because etanercept and MTX both affect clinical response, it is difficult to suggest whether MTX has a synergetic effect on etanercept treatment in this study design. Hyrich and colleagues used a comparable study design to our study, although, another outcome measurement than MDA was used and follow-up was only 6 months (12). Furthermore, their study population had a higher disease activity making a comparison difficult (12). In our study, no significant differences were found in sustained MDA between patients treated with etanercept with and without concomitant MTX. This could suggest that MTX has no significant synergetic effect on etanercept treatment.

In this study, patients treated with adalimumab and concomitant MTX were more likely to achieve sustained MDA than without MTX. The results in adalimumab treatment correspond to previous studies, including a randomised controlled trial (RCT) and a cohort study (11, 14). The cohort study of Heiberg and colleagues used similar inclusion criteria like our study. However, follow-up time was 6 months and, as a result, only MDA was a feasible endpoint instead of sustained MDA (11). They showed that 5.5% of the patients without MTX and 15.6% of the patients with concomitant MTX achieved MDA after 6 months (p=0.07).

The role of antibody formation against adalimumab could explain the synergetic effect of MTX in adalimumab treatment. Patients treated with adalimumab and concomitant MTX less frequently develop substantial amounts of antibodies and obtain higher adalimumab concentrations (3, 4, 6, 7). Conversely, etanercept is only marginally immunogenic and, to our knowledge, no data regarding the effect of concomitant MTX use on etanercept

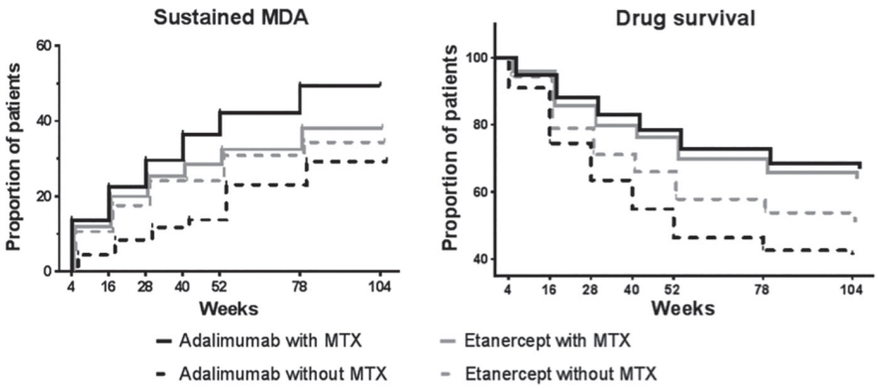

Fig. 1. Survival curve of patients achieving sustained RA and drug survival in etanercept and adalimumab treatment with or without concomitant MTX.

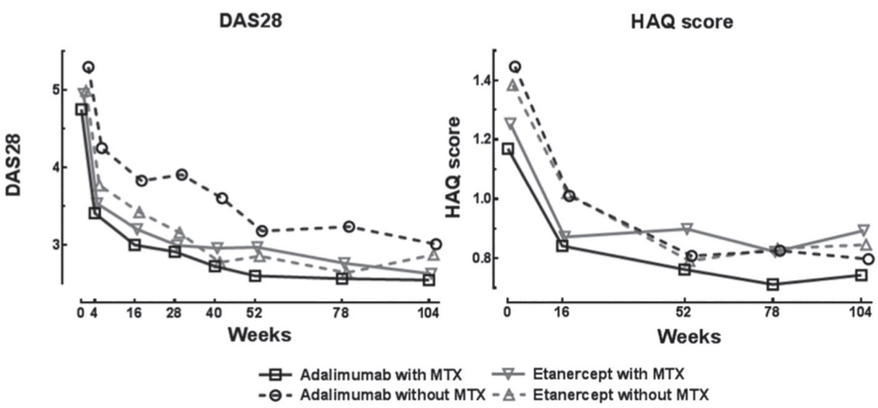

Fig. 2. Mean DAS28 and HAQ score over time.

concentration is currently available. The beneficial effect of concomitant MTX in achieving a good clinical response found in adalimumab treated patients, but not in etanercept treated patients, could possibly be explained by difference in immunogenicity. However, measurements of drug concentrations and anti-drug antibodies were not included in this study, thus, other explanations cannot be excluded. Discontinuation rate was significantly lower for patients using concomitant MTX *versus* without in both adalimumab and etanercept treatment. Compared to a recent study of Zhang and colleagues we found higher hazard ratios. Presumably because Zhang and colleagues excluded patients who discontinued treatment within the first 120 days after the start of the biological (16). In our study, The discontinuation rate was already more than 40% of total discontinuation after 16 weeks (adalimumab without MTX 26% out of 56%, with MTX 13% out of 31%, etanercept without MTX 22% out of 48% and with MTX 15% out of 35%), which could explain the higher hazard ratios for discontinuation.

Beside sustained MDA and biological discontinuation, ΔDAS28 and ΔHAQ were analysed. The average decrease in DAS28 was higher in adalimumab treated patients with concomitant MTX compared to without MTX. The difference in adalimumab treatment was the strongest in the first 16 weeks, but was also significant in the weeks thereafter. Because the difference was rather small (0.57 (p<0.001)) the clinical relevance is limited. No significant differences were found in etanercept treatment with *versus* without concomitant MTX, even when the data was split. Hyrich and colleagues also found a small difference in ΔDAS28 between patients treated with etanercept and MTX (ΔDAS28 of -2.3) *versus* without MTX (ΔDAS28 of 2.0) (12). A larger difference was found by Heiberg and colleagues. They showed that after 6 months the DAS28 decreased with 0.61 points in adalimumab treated patients without MTX and 1.66 points in the group treated with MTX (p=0.001) (11). In our study, functional ability decreased not significantly different between subgroups in both adalimumab and etanercept treatment. Another cohort study found small differences in ΔHAQ between patients treated with and without concomitant MTX (11). Due to the missing data in HAQ, only 4 measurement points could be used. In both HAQ and DAS28 analysis no imputation methods were used, which resulted in a responder analysis.

Caution must be taken to implement our results directly into treatment regimes. In contrast to etanercept, adalimumab treated patients without MTX had a significantly worse disease status at the start of the biological agent. Although the results were adjusted for baseline differences in disease status, confounding by indication could affect treatment response. In this study, subgroups were based on MTX use on baseline. However, unknown changes in MTX during follow-up could have affected treatment response. Furthermore, no distinction was made in DMARD use other than MTX. Other studies showed no differences in clinical response and discontinuation rate between combination therapy with MTX and with other DMARDs (10, 12, 13). Therefore, a significant impact of other DMARDs seems unlikely. No cohort studies, however, with long-term follow-up and sustained MDA as outcome measures were performed in these subgroups. In this study, clinical response and drug survival were used to give an overview of treatment response. Radiographic outcome measurements could be of added value in this overview, but were not available for this study. Interesting would be to compare adalimumab and etanercept head-to-head, but the adalimumab cohort and etanercept cohort were not designed to compare with each other despite the similar set up of the two cohorts. Therefore, these statistics are lacking in this study.

Several studies suggest the importance of concomitant MTX use in adalimumab and etanercept treatment. Whether

MTX is used directly before start of biological treatment or not affects the results and studies should, therefore, be interpreted differently. This long-term study included patients who were treated with MTX before start of biological treatment. Therefore, a synergetic effect of MTX on biological treatment could be studied. In this study, we can conclude that treatment discontinuation was lower in patients treated with concomitant MTX in both adalimumab and etanercept treatment. However, considering good clinical response, contrasting to etanercept, only in adalimumab treatment a synergetic effect of MTX is observed.

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