EXTENDED REPORT

Adalimumab and methotrexate is more effective than adalimumab alone in patients with established rheumatoid arthritis: results from a 6-month longitudinal, observational, multicentre study

M S Heiberg, E Rødevand, K Mikkelsen, C Kaufmann, A Didriksen, P Mowinckel, T K Kvien

Ann Rheum Dis 2006;**65**:1379–1383. doi: 10.1136/ard.2006.051540

See end of article for authors' affiliations

Correspondence to: M S Heiberg, Department of Rheumatology, Diakonhjemmet Hospital, Box 23 Vinderen, N-0319 Oslo, Norway; marte.schrumpf@diakonsysk.no

Accepted 1 May 2006
Published Online First
5 May 2006

Objectives: To compare the effectiveness of adalimumab monotherapy and adalimumab and methotrexate (MTX) combination therapy in patients with established rheumatoid arthritis.

Methods: Data from an ongoing longitudinal observational study in Norway were used to compare response to treatment with two different adalimumab regimens (monotherapy, n=84; combination with MTX, n=99). Patients were assessed with measures of disease activity, health status and utility scores. Within-group changes were analysed from baseline to follow-up at 3 and 6 months and the changes were compared between groups after adjustment for the propensity score. The groups were also compared for the proportions of patients achieving European League Against Rheumatism (EULAR) good response, Disease Activity Score (DAS)28 remission and treatment terminations.

Results: The improvement from baseline was significant for all measures in the adalimumab and MTX group, but only for DAS28, joint counts, two Short-form Health Survey with 36 questions (SF-36) dimensions and patient's and investigator's global assessment in the monotherapy group. All between-group differences were numerically in favour of combination therapy and significant for C reactive protein, joint counts, DAS28, Modified Health Assessment Questionnaire, investigator's global assessment, four SF-36 dimensions and Short Form 6D at 6 months. More patients in the combination therapy group reached EULAR good response ($p<0.001$) and remission ($p=0.07$). At 6 months, 80.8% of the patients in the combination therapy group and 59.5% in the monotherapy group remained on treatment ($p=0.002$). More withdrawals in the monotherapy group were due to adverse events.

Conclusions: Our results were consistent across several categories of end points and suggest that adalimumab combined with MTX is effective in patients with rheumatoid arthritis treated in daily clinical practice and is superior to adalimumab monotherapy.

Great progress has been made in the management of rheumatoid arthritis over the past years, including better treatment strategies¹ and access to biological agents in patients who fail to benefit from traditional disease-modifying antirheumatic drugs (DMARDs).² Randomised controlled trials (RCTs) of etanercept and adalimumab have shown efficacy for monotherapies^{3–4} as well as for regimens combining the anti-tumour necrosis factor (TNF) drugs with methotrexate (MTX).^{5–6} It has been established that infliximab should be given in combination with MTX.⁷ Some studies have shown that etanercept in combination with MTX provides larger benefits than monotherapy, both on clinical^{8–9} and radiographic end points.¹⁰ One RCT in MTX-naïve patients with recent onset rheumatoid arthritis has also shown that adalimumab in combination with MTX was superior to adalimumab alone,¹¹ but comparative analyses of the effectiveness of adalimumab with and without MTX have not been carried out in patients with established disease.

Strict inclusion criteria and short duration of trials may limit the external validity of results from RCTs.^{12–13} A longitudinal observational study (LOS) is the preferred design for studying effectiveness, which refers to how well a drug performs under real-life conditions outside the context of an RCT.¹⁴ A register of DMARD prescriptions for patients with inflammatory arthropathies has been established in

Norway, which provides an opportunity to compare effectiveness across treatment regimens in a real-life setting. We compared the effectiveness of adalimumab and MTX versus adalimumab alone in patients with rheumatoid arthritis.

MATERIALS AND METHODS

Setting

Five Norwegian rheumatology departments have, from December 2000, consecutively included all patients with inflammatory arthropathies, starting with a new DMARD regimen, in the Norwegian-DMARD register. The study design is a phase IV, multicentre, LOS. Demographic variables were recorded at baseline and patients were assessed at baseline, after 3, 6 and 12 months, and then yearly with core measures of disease activity and health-status measures. The completeness of the register is about 85%. By January 2005, 4347 cases were enrolled.

Abbreviations: DAS, Disease Activity Score; DMARD, disease-modifying antirheumatic drug; EULAR, European League Against Rheumatism; LOS, longitudinal observation study; MTX, methotrexate; RCT, randomised controlled trial; SF-36, Short-form Health Survey with 36 questions; SF-6D, Short Form 36; SRM, standardised mean response; TNF, tumour necrosis factor; VAS, Visual Analogue Scale

Patients

Patients were eligible for the present analyses if they had rheumatoid arthritis (ie, a given International Classification of Diseases-10 diagnosis of M05.8, M05.9 or M06.0) and were treated with adalimumab (usually 40 mg subcutaneous every other week), with or without concomitant MTX (fig 1). The eligibility criteria were met by 183 patients (mean standard deviation (SD) age 54 (14) years, disease duration 12.6 (9.7) years), of whom 79% were women, 76.1% were rheumatoid factor positive, 80.3% had erosive disease and 33.3% had rheumatoid nodules. In all, 84 patients received adalimumab monotherapy and 99 patients received adalimumab and MTX (mean dose 13 mg/week). The patients in the two groups had similar baseline demographic and disease characteristics, with the exception of the number of previous DMARD regimens and dose of concomitant use of prednisolone (table 1). Further, 90.5% of the patients in the adalimumab monotherapy group and 56.6% of the patients in the combination therapy group had previously used MTX monotherapy. Among these, more patients in the monotherapy group (69%) than in the combination therapy group (16%) discontinued MTX due to adverse events. In all, 46% of the patients in the monotherapy group and 42% in the combination group had previously been using infliximab or etanercept ($p=0.29$). Disease activity and health status variables at baseline were similar in the two groups (tables 2 and 3). Eighteen (9.8%) patients withdrew before the 3-month assessment and were not included in the analyses: 8 patients (2 lack of efficacy, 1 cancer, 1 transferred to other hospital, 4 unknown) in the monotherapy group versus 10 patients (2 lack of efficacy, 5 adverse events, 3 unknown) in the combination therapy group.

The patients gave written informed consent before participation. The study was approved by the regional ethics committee, and the storage of data was approved by the Data Inspectorate.

Figure 1 Patient selections from the Norwegian-disease-modifying antirheumatic drug (NOR-DMARD) register. The flowchart shows how patients from the NOR-DMARD register were selected for the present analyses. AS, ankylosing spondylitis; DMARD, disease-modifying antirheumatic drug; JA, juvenile arthritis; LOCF, last observations carried forward; MTX, methotrexate; PsA, psoriatic arthritis; RA, rheumatoid arthritis.

Table 1 Baseline demographic and disease variables in the two treatment groups

	Adalimumab (n = 84)	Adalimumab and MTX (n = 99)	p Value
Age (years)	56.1 (12.9)	52.4 (14.4)	0.07
Women	78.6	78.8	0.97
Disease duration (years)	13.5 (9.7)	11.8 (9.7)	0.26
No of previous DMARDs	4.9 (2.5)	3.8 (3.2)	0.01
Erosive disease	87.8	78.9	0.12
Rheumatoid factor positive	79.8	73.5	0.32
Corticosteroid dose (mg)	5.4 (4.7)	3.4 (4.1)	<0.01
Previous use of MTX	90.5	56.6	<0.001

DMARDs, disease-modifying antirheumatic drugs; MTX, methotrexate. Values are presented as mean (SD) for continuous variables and as % for categorical variables.

Assessments

Patients were assessed at baseline and after 3 and 6 months with core measures of disease activity,¹⁵ but also by additional health status measures. The 28-joint counts were carried out partly by rheumatologists and partly by trained study nurses. DAS28 is a composite measure, based on 28 tender and swollen joint counts, patient's global assessment on a 100-mm Visual Analogue Scale (VAS) and the erythrocyte sedimentation rate (ESR).¹⁶ EULAR good response is defined as a change in DAS28 score >1.2 and $\text{DAS28} \leq 3.2$ at follow-up.¹⁷ Remission is defined as $\text{DAS28} < 2.6$.¹⁸ Modified Health Assessment Questionnaire is a modified version of HAQ,¹⁹ with a score from 1 to 4 (4, worst disability). Medical Outcomes Study Short-form Health Survey with 36 questions (SF-36)²⁰ is a commonly used health status measure. It contains 36 questions measuring health across eight different dimensions—physical functioning, role limitations due to physical health problems, bodily pain, vitality, social functioning, role limitations due to emotional problems, mental health and general health. A score is computed in each dimension with a value from 0 (worst possible health state) to 100 (best possible health state). Short Form 6D (SF-6D) is a utility score based on SF-36, and was computed according to a published algorithm.²¹ The score ranges from 0 (dead) to 1 (perfect health).

Analyses

Baseline values were compared between the adalimumab monotherapy group and the combination therapy group using two-sample t tests (continuous variables) and χ^2 tests (categorical variables). Within-group changes from baseline to the 3-month and 6-month follow-up assessments were examined by a paired samples t test. Analyses of covariance (ANCOVA),²² with adjustments for the propensity score, were used to compare the changes between the groups and estimate the adjusted mean changes from baseline in the two groups.

The propensity score reflects the propensity for receiving combination therapy versus monotherapy. This statistical approach aims at overcoming the problem of confounding by indication in observational studies (not randomised). Different demographic and disease variables were entered in a logistic regression analysis and the covariates were retained in the model according to statistical significance. Prednisolone dose and MTX tolerability were the variables included in the propensity score. The groups were also balanced with respect to age and sex by including these variables in the propensity score regardless of statistical significance.

The magnitudes of change from baseline to follow-up examinations were expressed as standardised response

Table 2 Clinical variables at baseline and changes from baseline to 3-month and 6-month assessments after adjustments for the propensity score

	Baseline			3-month changes			6-month changes		
	Adalimumab (n = 84)	Adalimumab and MTX (n = 99)	p Value	Adalimumab (n = 76)	Adalimumab and MTX (n = 89)	p Value*	Adalimumab (n = 76)	Adalimumab and MTX (n = 89)	p Value*
ESR	34.6 (25.7)	29.5 (21.1)	0.16	-2.5 (22.1)	-4.6 (21.6)	0.61	-3.3 (21.4)	-8.1 (20.9)	0.21
CRP	28.7 (31.3)	27.0 (31.0)	0.73	-0.7 (37.0)	-11.7 (36.2)	0.11	-0.2 (28.0)	-14.0 (35.7)	0.03
SJC	8.4 (5.9)	9.7 (5.7)	0.12	-1.9 (5.9)	-5.4 (5.8)	0.001	-2.1 (6.5)	-6.1 (6.4)	<0.001
TJC	10.2 (7.5)	9.9 (7.2)	0.73	-1.1 (8.4)	-4.8 (8.3)	0.05	-2.5 (9.1)	-6.0 (8.8)	0.03
VAS p.	54.1 (24.3)	55.4 (23.6)	0.72	-9.2 (30.3)	-17.2 (29.7)	0.14	-8.3 (32.7)	-19.1 (32.0)	0.05
global									
VAS i.	49.4 (19.1)	48.6 (19.6)	0.78	-17.2 (24.7)	-22.7 (24.2)	0.21	-16.8 (26.7)	-25.9 (26.3)	0.04
global									
DAS28	5.5 (1.2)	5.4 (1.2)	0.60	-0.66 (1.6)	-1.44 (1.5)	0.01	-0.61 (1.7)	-1.66 (1.7)	0.001
M-HAQ	1.89 (0.57)	1.84 (0.45)	0.52	-0.09 (0.52)	-0.27 (0.52)	0.06	-0.11 (0.53)	-0.29 (0.53)	0.05

CRP, C reactive protein; DAS, Disease Activity Score; ESR, erythrocyte sedimentation rate; M-HAQ, Modified Health Assessment Questionnaire; SJC, swollen joint count (28 joints); TJC, tender joint count (28 joints); VAS, Visual Analogue Scale.

Values are presented as mean (SD).

*p Values are from analysis of covariance after adjustments for the propensity score.

means (SRM). The SRM values are calculated by dividing the change by the standard deviation (SD) of the change. SRM values were interpreted as effect sizes according to Cohen²³—that is, SRMs ≥ 0.2 and < 0.5 , ≥ 0.5 and < 0.8 , and ≥ 0.8 indicate small, moderate and large magnitudes of change, respectively.

Achievement of treatment success, defined as DAS28 EULAR good response and DAS28 remission, was analysed in the subset of patients with a baseline DAS28 score > 3.2 , as EULAR good response implies that the DAS28 score should be reduced to 3.2 or lower. Crude “drug survival” rates were assessed using Kaplan–Meier analysis, and the rates were compared with adjustment for the propensity score in a Cox regression analysis.

All changes were examined, with last observations carried forward when values were missing; at least one follow-up examination was required. A significance level of 5% was used in all the analyses. No correction for multiple comparisons was carried out. Statistical analyses were carried out with SPSS software V.12.0.

RESULTS

Tables 2 and 3 show the adjusted changes in disease activity and health status measures from baseline to 3 and 6 months. The improvements were consistently superior in the combination therapy group compared with the monotherapy group at 3 and 6 months and significant for CRP, joint counts, DAS28, Modified Health Assessment Questionnaire, investigator's global assessment, four SF-36 dimensions and SF-6D

at 6 months. Similar results were also seen without adjustments for the propensity score (results not shown).

The within-group analyses showed that the patients in the combination therapy group improved markedly from baseline to follow-up examinations at both 3 and 6 months for all measures (tables 2 and 3, p values not shown), whereas changes were significant only for DAS28, SF-36 role physical, SF-36 pain, swollen and tender joint counts, VAS patient's global assessment and VAS investigator's global assessment in the monotherapy group. The mean reduction in corticosteroid use was similar in the two groups.

The magnitudes of treatment responses are displayed in fig 2. The SRM values in the adalimumab and MTX group were superior to those in the monotherapy group for all measures. Only the SRM for VAS investigator's global assessment exceeded 0.5 in the monotherapy group.

EULAR good response was reached by 13.7% and 38.2% ($p = 0.003$) of the patients in the monotherapy and combination therapy groups, respectively, at 3 months, and by 9.1% and 42.9% ($p < 0.001$) of the patients after 6 months. The corresponding proportions achieving remission were 7.8% versus 14.7% ($p = 0.25$) at 3 months and 5.5% versus 15.6% ($p = 0.07$) at 6 months.

The proportions remaining on drug treatment at 6 months were 60% in the adalimumab monotherapy group and 80% in the adalimumab and MTX group ($p = 0.002$; fig 3). The propensity score adjusted relative risk (RR; 95% CI) for discontinuing monotherapy versus combination therapy was 2.5 (1.3, 4.8) at 6 months. Treatment terminations were due

Table 3 Short-form Health Survey with 36 question scores at baseline and adjusted changes from baseline to the 6-month assessment

SF-36	Baseline			6-month changes		
	Adalimumab (n = 86)	Adalimumab and MTX (n = 97)	p Value	Adalimumab (n = 76)	Adalimumab and MTX (n = 89)	p Value*
Physical function	38.7 (24.8)	43.3 (21.5)	0.18	2.7 (24.3)	9.9 (23.9)	0.08
Role physical	16.1 (29.5)	15.6 (25.0)	0.90	14.1 (40.0)	22.6 (39.4)	0.21
Bodily pain	30.0 (16.3)	31.7 (16.8)	0.50	8.5 (21.8)	14.0 (21.5)	0.14
Vitality	37.5 (20.7)	35.6 (20.1)	0.54	1.9 (24.2)	12.3 (23.8)	0.01
Social function	56.4 (23.5)	61.7 (28.7)	0.18	4.9 (30.8)	14.3 (30.3)	0.08
Role emotional	52.6 (43.3)	55.4 (42.0)	0.66	-1.4 (49.0)	16.7 (48.1)	0.03
Mental health	71.2 (20.5)	70.0 (18.6)	0.68	-2.2 (18.7)	8.6 (18.4)	0.001
General health	45.3 (21.4)	45.7 (19.6)	0.89	-0.05 (19.0)	7.5 (18.6)	0.02
SF-6D	0.56 (0.10)	0.58 (0.11)	0.19	0.001 (0.11)	0.06 (0.11)	<0.01

MTX, methotrexate; SF-36, Short-form Health Survey with 36 questions; SF-6D, Short Form 6D.

Values are presented as mean (SD).

*p Values are from analysis of covariance after adjustments for the propensity score.

Figure 2 The magnitude of response at 3 and 6 months presented as standardised response mean (SRM) values (mean change from baseline/SD of the change, adjusted values from analysis of covariance). A, adalimumab; CRP, C reactive protein; DAS, Disease Activity Score; ESR, erythrocyte sedimentation rate; M-HAQ, Modified Health Assessment Questionnaire; MTX, methotrexate; SF-6D, Short Form 6D; SJC, swollen joint count (28 joints); TJC, tender joint count (28 joints); VAS, Visual Analogue Scale.

to lack of efficacy, adverse events or other reasons in 44%, 47% and 9%, respectively, in the monotherapy group compared with 39%, 34% and 27% in the combination group.

DISCUSSION

Our study suggests a greater effectiveness of adalimumab and MTX versus adalimumab monotherapy in patients with established rheumatoid arthritis. The between-group differences were consistently in favour of the combination therapy group across all examined end points—that is, changes in disease activity measures, health status and utility measures (tables 2 and 3), the proportions with treatment success (EULAR response and remission) and maintained drug treatment (fig 3). The magnitude of changes in the adalimumab monotherapy group was actually small to moderate (fig 3).

In the randomised, controlled PREMIER study,¹¹ MTX-naïve patients with recent onset rheumatoid arthritis showed improvement with adalimumab both when given

as monotherapy and with concomitant MTX. However, responses were appreciably larger in the combination therapy group. The responses in both groups were of larger magnitude compared with those in our study. Although RCTs are essential when developing new treatment strategies, most patient cohorts in RCTs differ from the patients who are treated in routine care clinics, due to strict inclusion and exclusion criteria. LOS have a more flexible design and provide complementary information on drug performance under real-life conditions.¹⁴ For example, the patients with rheumatoid arthritis in our study had a mean disease duration of 12.6 years, had on average been using 4.3 previous DMARD regimens and as many as 44% of the patients had previously received other TNF-blocking agents. Thus, the present cohort is different from the patients who were enrolled in the PREMIER study.¹¹

Head-to-head comparisons between different adalimumab regimens have previously not been reported in established rheumatoid arthritis, but different adalimumab regimens have been compared with placebo in several RCTs.^{4, 6, 24, 25} These studies included patients with active and severe disease who had failed other DMARD treatment. van de Putte *et al*⁴ compared the efficacy and safety of adalimumab monotherapy to placebo. EULAR good response at 26 weeks was achieved by 8.5% of the patients (40 mg eow), which is similar to the EULAR good response rate in the monotherapy group in our study. An American College of Rheumatology 50 response was reached by 22.1% of the patients,⁴ whereas the American College of Rheumatology 50 response rates were as high as 40% and 55% in the active treatment arms in two placebo-controlled trials examining the efficacy of adalimumab and MTX.^{6, 25} The improvements in HAQ scores at 6 months were 0.38, 0.56 and 0.62, in the trials of monotherapy⁴ and adalimumab and MTX,^{6, 25} respectively. Changes in SF-36 scores in the trials of adalimumab and MTX^{6, 25} were of similar magnitude as in the combination therapy group in this study (table 3). Thus, even though we must exercise caution when comparing results of different RCTs, the results were consistently superior in the studies examining the efficacy of adalimumab and MTX^{6, 25} when compared with those in the monotherapy study.⁴ This difference is also supported by a recent Cochrane Review.²⁶

Figure 3 The proportion of patients remaining on treatment at 6 months, presented in a Kaplan-Meier plot ($p=0.002$). A, adalimumab; MTX, methotrexate.

A recent British LOS reported the use of adalimumab in 70 patients with rheumatoid arthritis.²⁷ The overall improvements in HAQ and DAS28 were 0.34 and 2.1, respectively. EULAR good response was reached by 26% of the patients, whereas 19% reached remission, and these rates are comparable to the observed responses in the combination therapy group in the present study. The patients who received adalimumab monotherapy performed better in the British study than in our study (25% reached EULAR good response).²⁷

An observational study should ideally include all patients. In our setting, about 15% of patients were lost due to inclusion failure, enrolment in RCTs or refusal to participate. The lack of randomisation in observational studies and potential channelling bias limit the opportunities to carry out adequate group comparisons. The problem can partly be overcome by using statistical approaches, of which propensity modelling is the contemporary method to adjust for channelling bias.²⁸ Another limitation to our study was the lack of radiographic data, as regular radiographic assessments were not feasible in the Norwegian-DMARD study. Retardation of joint destructions in radiographs has been shown with both etanercept and adalimumab when combined with MTX.^{10–25} However, radiographic outcome was also considerably better with adalimumab monotherapy than with methotrexate, despite the treatment groups having similar clinical response in the PREMIER study.¹¹

Treatment practice changes as new drugs are introduced and efficacy is documented through RCTs. However, observational studies also provide important information that is complementary to the controlled studies. It is established that infliximab should be given with MTX,⁷ and the superior efficacy of combination therapy has been shown for etanercept both in an RCT^{8–10} and in an observational study.⁹ Response rates in placebo-controlled trials with adalimumab seem to be greater with combination therapy,²⁶ and the effect of adalimumab and MTX was superior to that of adalimumab alone in the PREMIER study, including in patients with recent onset rheumatoid arthritis.¹¹ In line with the findings in the PREMIER study and the results from this real-life study of patients with established rheumatoid arthritis, we suggest that adalimumab should be combined with MTX whenever possible.

Authors' affiliations

M S Heiberg, P Mowinkel, T K Kvien, Department of Rheumatology, Diakonhjemmet Hospital, Oslo, Norway
E Rødevand, Department of Rheumatology, St Olav Hospital, Trondheim, Norway
K Mikkelsen, Department of Rheumatology, Lillehammer Hospital for Rheumatic Diseases, Lillehammer, Norway
C Kaufmann, Department of Rheumatology, Buskerud Central Hospital, Drammen, Norway
A Didriksen, Department of Rheumatology, University Hospital Northern Norway, Tromsø, Norway

Funding: Research grants for the NOR-DMARD study have been received from Abbott, Amgen, Wyeth, Aventis, MSD, Schering-Plough/Centocor and the Norwegian Directorate for Health and Social Affairs. The work was supported by The Norwegian Women's Public Health Association. No pharmaceutical company participated in study design, data collection, data handling or manuscript preparation.

Competing interests: MSH and TTK have received consultancies and invited speaker honoraria from different pharmaceutical companies that are marketing TNF-blocking agents. ER, KM, CK, AD and PM have no competing interests.

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