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

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Keywords.
Rheumatoid arthritis, adalimumab, propensity score, longitudinal observational study.

Abstract

Objectives. To compare the effectiveness of adalimumab monotherapy and adalimumab plus methotrexate in patients with established RA.

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. We analyzed within-group changes 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 EULAR good response, DAS-28 remission and treatment terminations.

Results. The improvement from baseline was statistically significant for all measures in the adalimumab + MTX group, but only for DAS-28, joint counts, 2 SF-36 dimensions and patient's and investigator's global assessment in the monotherapy group. All between-group differences were numerically in favor of combination therapy and statistically significant for CRP, joint counts, DAS-28, M-HAQ, investigator's global assessment, 4 SF-36 dimensions and SF-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 therapy (p=0.002). More withdrawals were due to adverse events in the monotherapy group.

Conclusions. Our consistent results across several categories of endpoints suggest that adalimumab combined with methotrexate is effective in RA patients treated in daily clinical practice and superior to adalimumab monotherapy.

Introduction

Great progress has been made in the management of RA over the last years including better treatment strategies [1] and access to biological agents that provide benefit to patients who fail traditional disease modifying anti-rheumatic drugs (DMARDs) [2]. Randomized controlled trials (RCTs) of etanercept and adalimumab have demonstrated efficacy for monotherapies [3;4] as well as for regimens combining the anti-TNF drugs with methotrexate (MTX)[5;6]. It has been established that infliximab should be administered 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 endpoints [10]. One RCT in MTX naïve patients with recent onset RA has also shown that adalimumab in combination with MTX was superior to adalimumab alone [11], but comparative analyses of the effectivenss of adalimumab with and without MTX have not been performed in patients with established disease.

Strict inclusion criteria and short duration of trials may limit the external validity of results from RCTs [12;13]. 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 a 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. The aim of this analysis was to compare the effectiveness of adalimumab plus MTX versus adalimumab alone in patients with RA.

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 NOR-DMARD register. The study design is a phase IV, multicenter, longitudinal, observational study. Demographic variables are recorded at baseline and patients are assessed at baseline, after 3, 6, 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.

Patients

Patients were eligible for the present analyses if they had RA (i.e. a given ICD-10 diagnosis of M05.8, M05.9 or M06.0) and were treated with adalimumab (usually 40 mg sc eow), with or without concomitant methotrexate (MTX) (figure 1). The eligibility criteria were met by 183 patients (mean (SD) age 54 (14) years, mean (SD) disease duration 12.6 (9.7) years, 79% were females, 76.1% were rheumatoid factor positive, 80.3% had erosive disease and 33.3% had rheumatoid nodules). 84 patients received adalimumab monotherapy and 99 patients received adalimumab plus MTX (mean dose 13 mg per 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 compared to 56.6% of the patients in the combination therapy group had previously used MTX monotherapy. Among these, more patients had discontinued MTX due to adverse events in the monotherapy group (69%) than in the combination therapy group (16%). 46 % of the patients in the monotherapy group and 42% in the combination group had previously been using infliximab and/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, 5 adverse events, 3 unknown) in the monotherapy group vs 10 patients (2 lack of efficacy, 1 cancer, 1 transferred to other hospital, 4 unknown) in the combination therapy group).

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

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 performed partly by rheumatologists and partly by trained study nurses. DAS-28 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 DAS-28 score >1.2 and DAS-28$\leq$3.2 at follow-up [17]. Remission is defined as DAS-28<2.6 [18]. M-HAQ is a modified version of HAQ [19] with a score from 1 to 4 (4 = worst disability). MOS 36-item short form health survey (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 within each dimension with a value from 0 (worst possible health state) to 100 (best possible health state). 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).

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Analyses

Baseline values were compared between the adalimumab monotherapy group and the combination therapy group using two-sample t-tests (continuous variables) and chi-square tests (categorical variables). Within-group changes from baseline to the 3-and 6-month follow-up assessments were examined by 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 randomized). Different demographic and disease variables were entered in a logistic regression analysis, and the covariates were kept in the model according to statistical significance. Prednisolone dose and MTX tolerability were the included variables in the propensity score. The groups were also balanced with respect to age and gender by including these variables in the propensity score regardless of statistical significance.

The magnitudes of change from baseline to follow-up examinations were also expressed as standardized response 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 Cohen [23], i.e. SRMs $\geq 0.2 < 0.5$, $\geq 0.5 < 0.8$ and ≥ 0.8 indicate small, moderate and large magnitudes of change, respectively.

Achievement of treatment success defined as DAS-28 EULAR good response and DAS-28 remission was analysed in the subset of patients with a baseline DAS-28 score >3.2, since EULAR good response implies that the DAS-28 score should be reduced to 3.2 or lower. Crude "drug survival" rates were assessed in a 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 (LOCF) when values were missing, with at least one follow-up examination being required. A significance level of 5% was used in all the analyses. No correction for multiple comparisons was performed. Statistical analyses were performed with SPSS software, version 12.0 (SPSS Inc., Chicago).

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 to the monotherapy group after both 3 and 6 months and statistically significant for CRP, joint counts, DAS-28, M-HAQ, investigator's global assessment, 4 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 revealed that the patients in the combination therapy group improved significantly from baseline to follow-up examinations at both 3 and 6 months for all measures (table 2 and 3, p-values not shown), whereas changes were statistically significant only for DAS-28, 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.

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The magnitudes of treatment responses are displayed in figure 2. The SRM values in the adalimumab + MTX group were superior to the SRM values 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% vs. 14.7% (p=0.25) at 3 months and 5.5% vs. 15.6% (p=0.07) at 6 months.

The proportions remaining on drug therapy at 6 months were 60% in the adalimumab monotherapy group and 80% in the adalimumab plus MTX group (p=0.002) (figure 3). The propensity score adjusted RR (95%CI) for discontinuing monotherapy vs. combination therapy was 2.5 (1.3, 4.8) at 6 months. Treatment terminations were due to lack of efficacy, adverse events or other reasons in 44%, 47% and 9%, respectively, in the monotherapy group compared to 39%, 34.% and 27% in the combination group.

Discussion

The present study suggests a superior effectiveness of adalimumab plus MTX versus adalimumab monotherapy in patients with established RA. The between-group differences were consistenly in favor of the combination therapy group across all examined endpoints, i.e. changes in disease activity measures, health status and utility measures (table 2 and 3), the proportions with treatment success (EULAR response and remission) and maintained drug therapy (figure 3). The magnitudes of changes in the adalimumab monotherapy group were actually small to moderate (figure 3).

In the randomized, controlled PREMIER study [11], adalimumab provided improvements in MTX-naïve patients with recent onset RA, both when given as monotherapy and with concomitant MTX. However, responses were significantly larger in the combination therapy group. The responses in both groups were of larger magnitude compared to 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. Longitudinal, observational studies (LOS) have a more flexible design, and provide complementary information on drug performance under real life conditions [14]. For example, the RA patients in our study had a mean disease duration of 12.6 years, had in average been using 4.3 previous DMARD regimens, and as much as 44% of the patients had previously received other TNF-blocking agents. Thus, the present cohort is very 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 RA, but different adalimumab regimens have been compared to placebo in several RCTs [4;6;24;25]. These studies included patients with active and severe disease who had failed other DMARD therapy. 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 the present study. An ACR50 response was reached by 22.1% of the patients [4], whereas the ACR50 response rates were as high as 40% and 55% in the active treatment arms in two placebo-controlled trials examining the efficacy of

adalimumab plus MTX [25;6]. The improvements in HAQ scores at 6 months were 0.38, 0.56 and 0.62, in the trials of monotherapy [4] and adalimumab+MTX [6;25], respectively. Changes in SF-36 scores in the trials of adalimumab+MTX [6;25] were of similar magnitude as in the combination therapy group in the present study (table 3). Thus, even if caution must always be applied when comparing results of different RCTs, the improvements were consistently superior in the studies examining the efficacy of adalimumab + MTX [6;25] than in the monotherapy study [4], and this difference is also supported by a recent Cochrane review [26].

A recent British LOS reported the use of adalimumab in 70 RA patients [27]. The overall improvements in HAQ and DAS-28 were 0.34 and 2.1, respectively. EULAR good response was reached by 26% of the patients, while 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% were lost either due to inclusion failure, enrolment in RCTs or refusal to participate The lack of randomization in observational studies and potential channelling bias limit the opportunities to perform 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 is the lack of radiographic data, as regular radiographic assessments were not feasible in the NOR-DMARD study. Retardation of joint destructions in radiographs has been demonstrated with both etanercept and adalimumab when combined with MTX [10;25]. However, radiographic outcome was also significantly superior with adalimumab monotherapy compared to methotrexate despite that these treatment groups had similar clinical response in the PREMIER study [11].

Treatment practice changes as new drugs are being introduced and efficacy is documented through RCTs. However, observational studies also provide important information that is complimentary to the controlled studies. It is established that infliximab should be given together with MTX [7], and the superior efficacy of combination therapy has been demonstrated for etanercept in both a RCT [8;10] and in an observational study [9]. Response rates in placebo controlled trials with adalimumab seem to be larger with combination therapy [26] and adalimumab + MTX was superior to adalimumab alone in the PREMIER study including patients with recent onset RA [11]. In line with the findings in the PREMIER study and the results from this real life study of patients with established RA, we suggest that adalimumab should be combined with MTX whenever possible.

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Association. No pharmaceutical company was involved in study design, data collection, data handling or manuscript preparation.

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

	Adalimumab (n=84)	Adalimumab + MTX (n= 99)	p-value
Age	56.1 (12.9)	52.4 (14.4)	0.07
Females	78.6	78.8	0.97
Disease duration, years	13.5 (9.7)	11.8 (9.7)	0.26
# 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 methotrexate	90.5	56.6	<0.001

Values are presented as mean (standard deviation of the mean) for continuous variables and as % for categorical variables. DMARDs = disease modifying anti-rheumatic drugs

Table 2. Clinical variables at baseline and changes from baseline to 3-and 6-month assessments after adjustments for the propensity score. Values are presented as mean (standard deviation of the mean). ESR=erythrocyte sedimentation rate, CRP= C-reactive proteine, SJC=Swollen

	Baseline			3-month changes			6-month changes		
	Adalimumab (n=84)	Adalimumab + MTX (n=99)	p-value	Adalimumab (n=76)	Adalimumab + MTX (n=89)	p-value*	Adalimumab (n=76)	Adalimumab + 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. global	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
VAS i. global	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
DAS-28	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

joint count (28 joints), TJC=tender joint count (28 joints), VAS=visual analogue scale, DAS=disease activity score, M-HAQ= modified health assessment questionaire

*P-values are from ANCOVA after adjustments for the propensity score.

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Table 3. SF-36 scores at baseline, and adjusted changes from baseline to the 6-month assessment.

SF-36	Baseline			6-month changes		
	Adalimumab (n=86)	Adalimumab+ MTX (n=97)	p-value	Adalimumab (n=76)	Adalimumab+ 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

Values are presented as mean (SD of the mean). SF-36=short form-36, SF-6D=short form-6D
*P-values are from ANCOVA after adjustments for the propensity score.

Figure legends

Figure 1.
Patient selections from the NOR-DMARD register.
The flowchart shows how patients from the Norwegian DMARD register were selected for the present analyses. RA=rheumatoid arthritis, AS=ankylosing spondylitis, JA=juvenile arthritis, PsA=psoriatic arthritis, MTX=methotrexate

Figure 2.
The magnitude of response at 3 and 6 months presented as SRM values (mean change from baseline/SD of the change, adjusted values from ANCOVA). SRM=standardized response mean, A=adalimumab, ESR=erythrocyte sedimentation rate, CRP= C-reactive protein, SJC=Swollen joint count (28 joints), TJC=tender joint count (28 joints), VAS=visual analogue scale, DAS=disease activity score, M-HAQ= modified health assessment questionnaire, SF-6D=short form-6D

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

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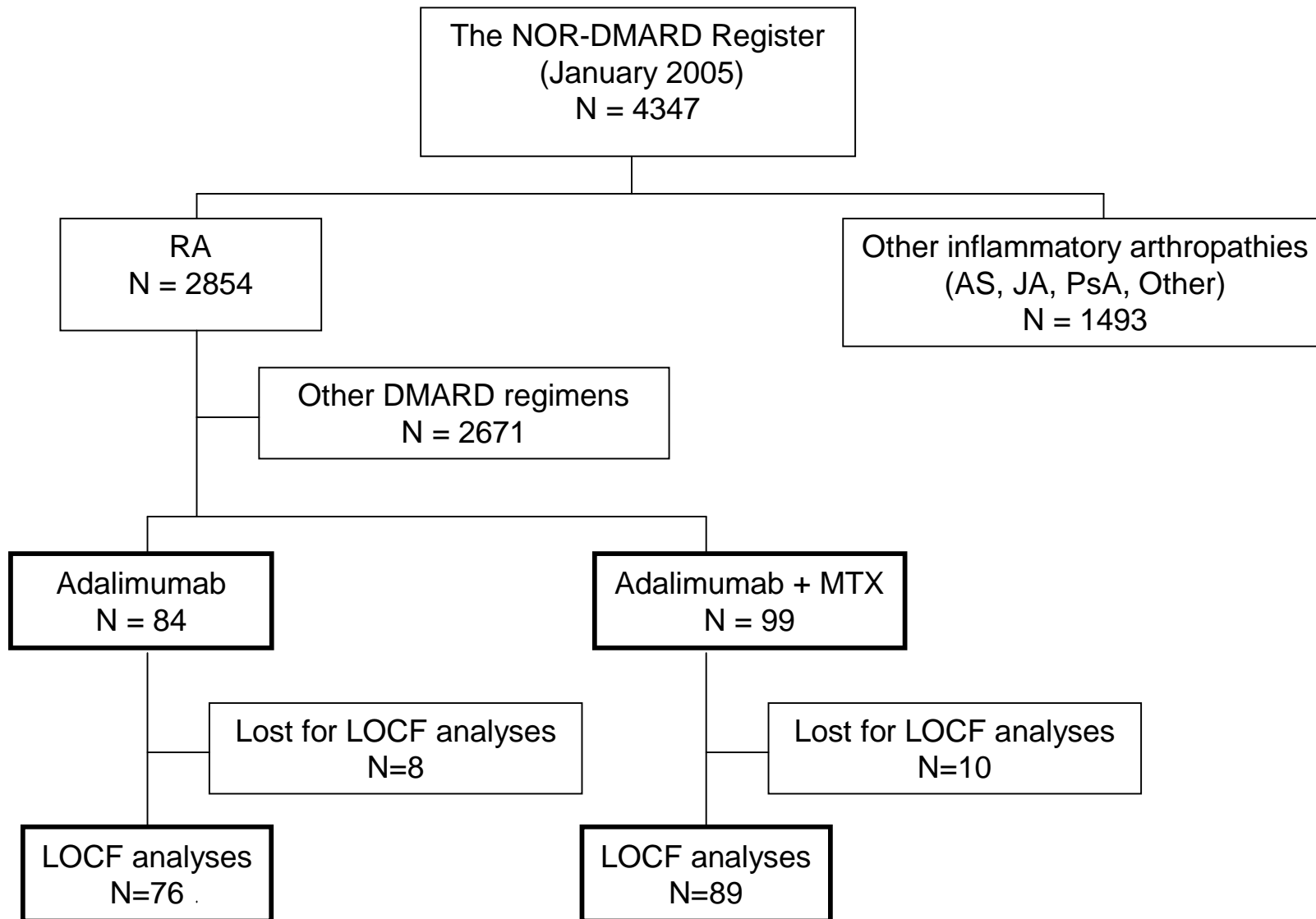
Figure 1.
The flowchart shows how patients from the Norwegian DMARD register were selected for the present analyses.
RA=rheumatoid arthritis, AS=ankylosing spondylitis, JA=juvenile arthritis, PsA=psoriatic arthritis, MTX=methotrexate, LOCF= last observation carried forward
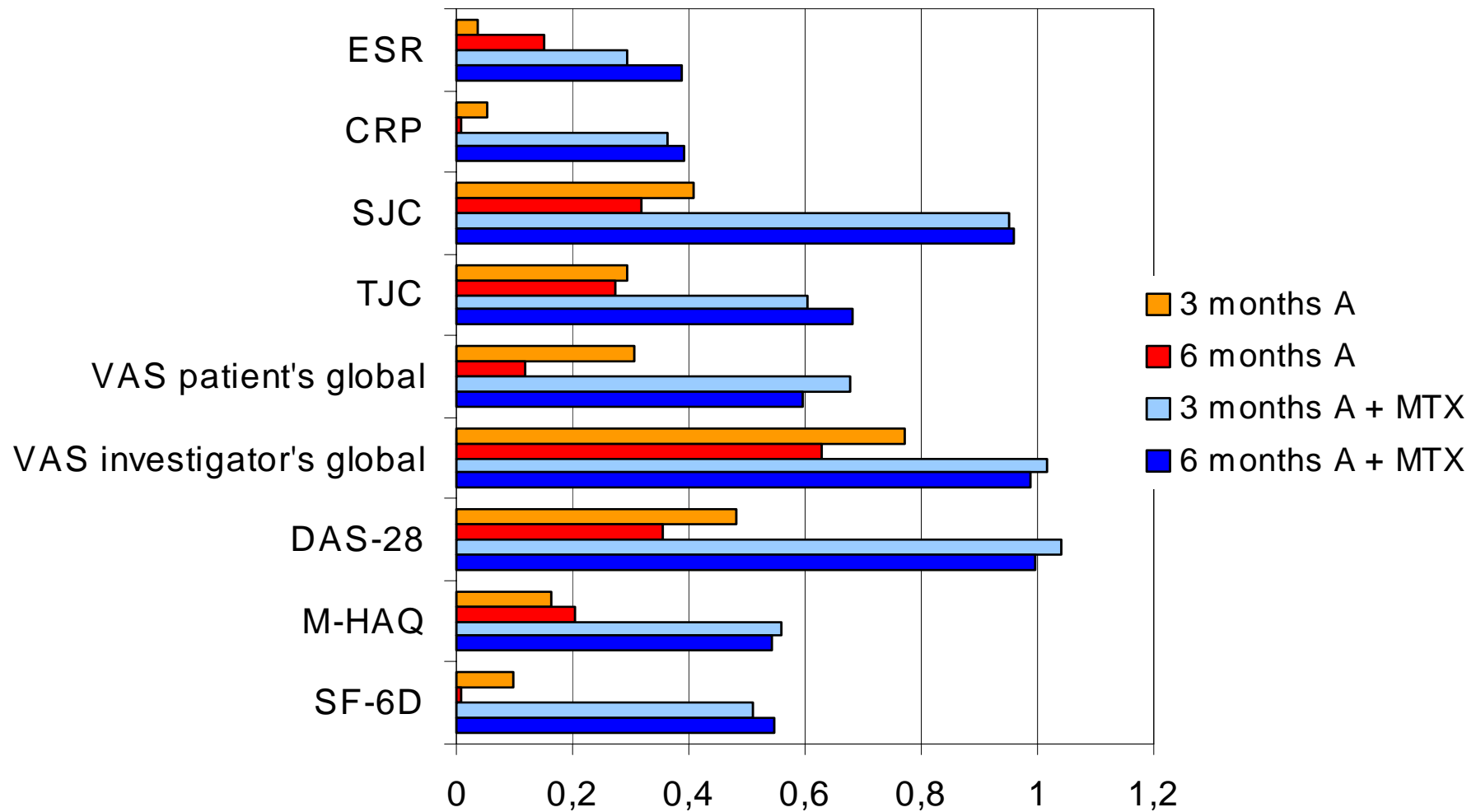
Figure 2.
The magnitude of response at 3 and 6 months presented as SRM values (mean change from baseline/SD of the change, adjusted values from ANCOVA). SRM=standardized response mean, A=adalimumab, ESR=erythrocyte sedimentation rate, CRP=C-reactive protein, SJC=Swollen joint count (28 joints), TJC=tender joint count (28 joints), VAS=visual analogue scale, DAS=disease activity score, M-HAQ=modified health assessment questionnaire, SF-6D=short form-6D
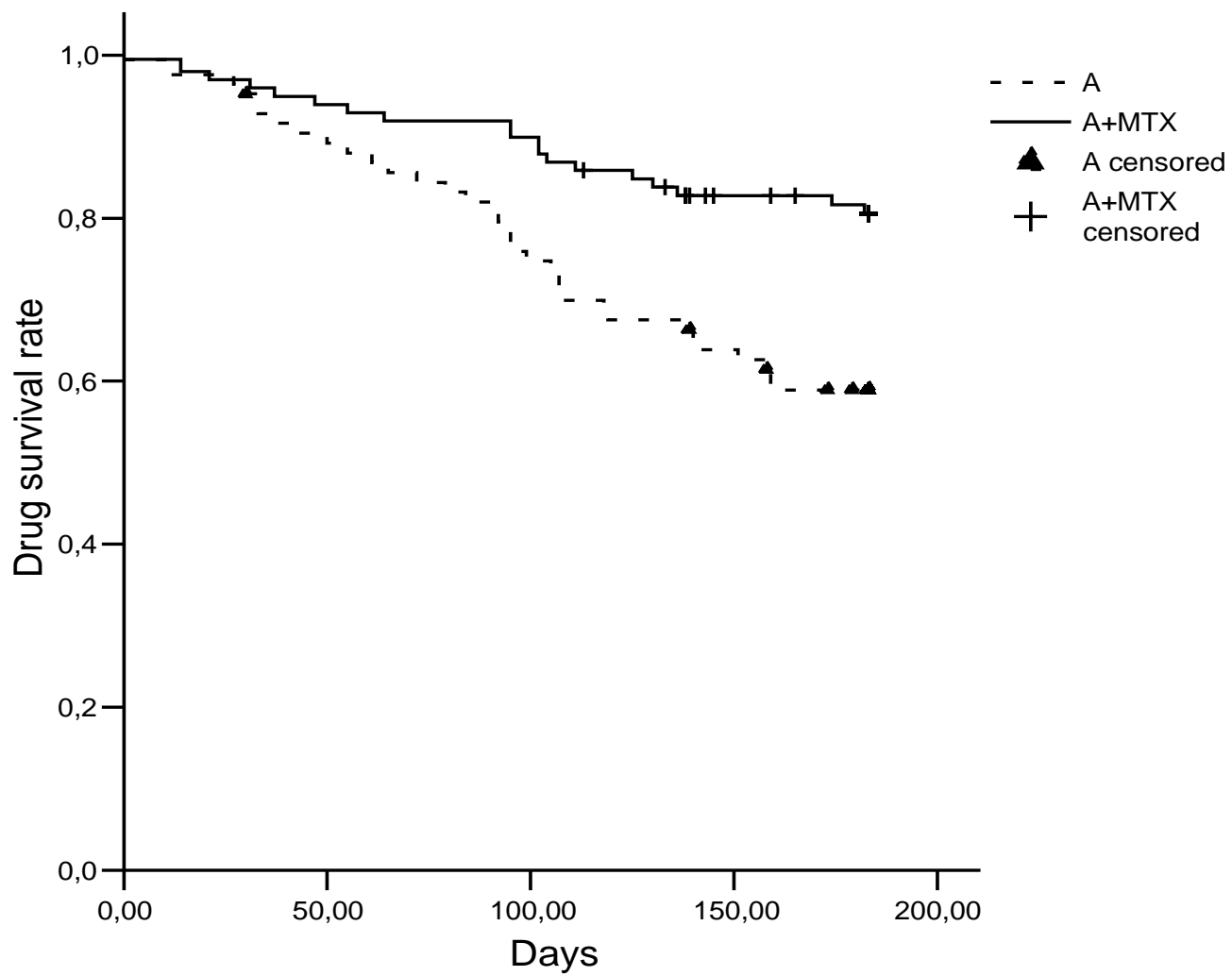
Figure 3.
The proportion of patients remaining on therapy at 6 months, presented in a Kaplan-Meier plot (p= 0.002). A=adalimumab