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EXTENDED REPORT

Adalimumab added to a treat-to-target strategy with methotrexate and intra-articular triamcinolone in early rheumatoid arthritis increased remission rates, function and quality of life. The OPERA Study: an investigator-initiated, randomised, double-blind, parallel-group, placebo-controlled trial

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ABSTRACT

Objectives An investigator-initiated, double-blinded, placebo-controlled, treat-to-target protocol (Clinical Trials:NCT00660647) studied whether adalimumab added to methotrexate and intra-articular triamcinolone as first-line treatment in early rheumatoid arthritis (ERA) increased the frequency of low disease activity (DAS28CRP<3.2) at 12 months.

Methods In 14 Danish hospital-based clinics, 180 disease-modifying anti-rheumatic drugs (DMARD)-naïve ERA patients (<6 months duration) received methotrexate 7.5 mg/week (increased to 20 mg/week within 2 months) plus adalimumab 40 mg every other week (adalimumab-group, n=89) or methotrexate +placebo-adalimumab (placebo-group, n=91). At all visits, triamcinolone was injected into swollen joints (max. four joints/visit). If low disease activity was not achieved, sulfasalazine 2 g/day and hydroxychloroquine 200 mg/day were added after 3 months, and open-label biologics after 6–9 months. Efficacy was assessed primarily on the proportion of patients who reached treatment target (DAS28CRP<3.2). Secondary endpoints included DAS28CRP, remission, Health Assessment Questionnaire (HAQ), EQ-5D and SF-12. Analysis was by intention-to-treat with last observation carried forward.

Results Baseline characteristics were similar between groups. In the adalimumab group/placebo group the 12-month cumulative triamcinolone doses were 5.4/7.0 ml (p=0.08). Triple therapy was applied in 18/27 patients (p=0.17). At 12 months, DAS28CRP<3.2 was reached in 80%/76% (p=0.65) and DAS28CRP was 2.0 (1.7–5.2) (medians (5th/95th percentile ranges)), versus 2.6 (1.7–4.7) (p=0.009). Remission rates were: DAS28CRP<2.6: 74%/49%, Clinical Disease Activity Index≤2.8: 61%/41%, Simplified Disease Activity Index<3.3: 57%/37%, European League Against Rheumatism/American College of Rheumatology Boolean: 48%/30% (0.0008<p<0.014, number-needed-to-treat: 4.0–5.4). Twelve months HAQ, SF12PCS and

EQ-5D improvements were most pronounced in the adalimumab group. Treatments were well tolerated.

Conclusions Adalimumab added to methotrexate and intra-articular triamcinolone as first-line treatment did not increase the proportion of patients who reached the DAS28CRP<3.2 treatment target, but improved DAS28CRP, remission rates, function and quality of life in DMARD-naïve ERA.

INTRODUCTION

During the past two decades, early and aggressive treatment of rheumatoid arthritis (RA) with disease-modifying antirheumatic drugs (DMARD) has significantly reduced the effects of the disease in terms of joint damage and disability.¹ Today, remission is an achievable goal in many patients, irrespective of the type of DMARD used, whether synthetic or biological.² However, the optimal treatment strategy in early RA is still debated, and issues such as initial mono versus combination therapy and the role of glucocorticoids and biologics are still disputed.³

In the Cyclosporine, Methotrexate and intra-articular Steroid in early Rheumatoid Arthritis study (CIMESTRA) study, we reported that aggressive intervention with methotrexate combined with intra-articular glucocorticoid injections into swollen joints effectively controlled disease activity and halted radiographic progression over 5 years of follow-up in early RA.^{4–6} This low-cost strategy yielded results which are comparable with those reported for biologics as first-line therapy.^{7–12} Thus, it has been speculated that these favourable results are attributable to a treat-to-target strategy rather than superiority of any specific drug.¹³

The current Optimised treatment algorithm in Early Rheumatoid Arthritis (OPERA) study aimed to investigate whether the results of a CIMESTRA

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strategy using a strict step-up methotrexate protocol combined with intra-articular glucocorticoids immediately following diagnosis with the aim of no swollen joints could be further improved by adding a tumour necrosis factor inhibitor (TNFi) as first-line therapy. Thus, inflammatory control was the aim in both treatment arms. The proportion of patients achieving DAS28CRP $<$ 3.2 at 12 months was the primary outcome and DAS28CRP, remission criteria, Health Assessment Questionnaire (HAQ), EQ-5D and SF-12 were the secondary endpoints.

MATERIALS AND METHODS

From August 2007 through December 2009, 180 DMARD-naïve and steroid-naïve patients with early RA were recruited consecutively from 14 outpatient clinics at rheumatology departments in Denmark and included in the OPERA study. Patients were aged over 17 years, fulfilled the American College of Rheumatology (ACR) 1987 revised criteria for RA, had a disease duration (from first persistently swollen joint) of less than 6 months, and moderate to severe RA defined as DAS28CRP (4 variables, C-reactive protein (CRP)-based) $>$ 3.2. Important exclusion criteria were treatment with glucocorticoids within the last 4 weeks, previous DMARD therapy, latent tuberculosis or previous malignancy. A complete list of exclusion criteria can be found at <http://www.clinicaltrials.gov> NCT00660647. Patients were randomised in blocks of four from a central, computer-generated list of study numbers.

Ethics

All patients gave written informed consent before enrolment. The protocol was approved by the Danish Medical Agency (2612-3393), the Danish Data Protection Agency (2007-41-0072) and the Regional Ethics Committee (VEK-20070008). The trial was undertaken in accordance with the Declaration of Helsinki, and carried out according to the principles of the International Conference on Harmonisation guidelines for Good Clinical Practice (GCP, 1996 revision) in the European Community under an independent contract research organisation by the Danish University GCP units (<http://www.gcp-enhed.dk>).

Study design and data collection

The OPERA study was an investigator-initiated, randomised, double-blind, placebo-controlled, two-armed, parallel-group, multicentre trial.

The patients were randomised into two, double-blinded treatment groups: The 'adalimumab-group' started oral methotrexate, 7.5 mg/week at baseline, increased to 15 mg/week after 1 month and 20 mg/week after 2 months (or the highest tolerated dose) in combination with adalimumab 40 mg subcutaneously every second week. The 'placebo-group' received the same treatment, except that adalimumab was replaced with placebo-adalimumab.

In both groups, any swollen joint observed at baseline or at a subsequent visit was injected with triamcinolone hexacetonide (40 mg/ml, 0.5–2 ml/joint). Up to four joints (max. 4 ml) could be injected per visit.

The patients were seen at scheduled study visits at baseline, 1, 2, 3, 6, 9 and 12 months. Between the scheduled visits, patients were contacted by phone (fortnightly the first 3 months, every month thereafter) and interviewed about signs of disease activity and adverse events, in which case an extra visit was scheduled.

If unacceptable disease activity persisted at the 3 months' visit or thereafter, that is, *either* 'DAS28CRP \geq 3.2 and \geq 1 swollen joint' or 'intra-articular injection of 4 ml triamcinolone had been given monthly for 3 consecutive months',

hydroxychloroquine (200 mg/day) and sulphasalazine (2 g/day) were added. If the treatment target (low disease activity, see next section) was not achieved within an additional 3 months, adalimumab/placebo-adalimumab was discontinued, the patient was considered a non-responder and excluded from the study, and open label biologics (other than adalimumab) were prescribed at the discretion of the treating physician. Blinding was maintained throughout the study period.

The primary outcome was the proportion of patients in each group that had achieved low disease activity (DAS28CRP $<$ 3.2) at 12 months. Secondary outcomes included DAS28CRP at 12 months, the proportions of patients who at 12 months achieved: DAS28 remission (DAS28CRP $<$ 2.6),¹⁴ Clinical Disease Activity Index (CDAI) remission (CDAI \leq 2.8),¹⁵ Simplified Disease Activity Index (SDAI) remission (SDAI $<$ 3.3),¹⁶ ACR/European League Against Rheumatism (EULAR) 28/40 Boolean remission,¹⁶ and absence of disability measured by HAQ and Short Form 12-item Survey SF-12v2 Health Survey (S12)-physical component score (PCS).^{17–18} Other secondary endpoints included quality of life (European Quality of Life 5 Dimensions (EQ-5D) and SF12-mental component score (MCS)). We used a modified version of EQ-5D with five levels of severity and the Danish Scoring algorithm with linear extrapolation between score dimensions (EQ-5D-5L).¹⁹ The cumulative dose of triamcinolone and the number and type of serious adverse events (SAE) were recorded.

Patient-reported outcomes (HAQ, Visual Analogue Scale (VAS) for pain, fatigue and global, SF12 and EQ-5D) were collected on touch screens in the waiting room.²⁰ The doctor recorded number of swollen and tender joints ($n=40$: metacarpophalangeal, proximal-interphalangeal, wrists, elbows, shoulder, knees, metatarsophalangeal and ankle joints), doctor's global score (VAS), monitored adverse events, prescribed medication and gave joint injections. Efforts were made to ensure that the same doctor followed each patient. CRP was measured using CRP QUICK-READ (Orion Diagnostica—range 8–160 mg/l).²¹

All patients received folic acid (5–10 mg/week) and oral calcium with vitamin D (1.000 mg calcium+800 IU vitamin D daily). At baseline, treatment with alendronate 70 mg/week was initiated according to national guidelines. Mild analgesics (acetaminophen) were allowed, but not non-steroidal anti-inflammatory drugs (NSAID), muscle relaxants or other analgesics.

Statistical analysis

A study size of 180 patients was chosen based on the assumption that 90% of patients in the adalimumab-group and 70% of patients in the placebo-group would achieve the primary endpoint. A total of 89 patients per treatment arm (dropout ratio 20%) gave 80% power to demonstrate a significant ($p=0.05$) difference in response rates.

Analysis was by intention-to-treat (ITT). All patients who received at least one injection with adalimumab or placebo-adalimumab were included. Last observation carried forward (LOCF) was applied for patients who withdrew from the trial before the 12-month visit. In a posthoc analysis, non-responder imputation (NRI) of the patients who withdrew from the study was performed for the primary outcome. ITT analysis without LOCF and completers' analysis were also performed and gave similar results (not shown).

Data are presented as medians (5th/95th percentile ranges), unless otherwise stated. Comparisons between groups were made with Fisher's exact test (dichotomous responses) and Mann-Whitney U test (non-dichotomous). Number-needed-to-treat (NNT) was calculated for achievement of remission.

Table 1 Baseline demographic, clinical and laboratory characteristics of the study population

	Adalimumab group (n=89)	Placebo group (n=91)	p Value between groups
Age (years)	56.2 (25.8–77.6)	54.2 (28.3–76.7)	0.71
Female sex (%)	63	69	0.46
Disease duration (days)	88 (42–162)	83 (42–150)	0.74
Rheumatoid factor positive (%)	70	74	0.67
Anti-CCP positive (%)	60	70	0.17
Number of tender joints (0–40)	15 (5–38)	16 (6–34)	0.78
Number of swollen joints (0–40)	10 (3–33)	11 (3–31)	0.66
VAS-doctors global (0–100 mm)	57 (27–89)	51 (22–86)	0.10
VAS-pain (0–100 mm)	63 (13–98)	58 (13–92)	0.21
VAS-patient global (0–100 mm)	70 (12–100)	65 (17–96)	0.27
VAS-patient fatigue (0–100 mm)	67 (9–94)	54 (9–92)	0.12
s-CRP (7–161 mg/l)	15 (7–133)	15 (7–109)	0.54
DAS28CRP (1.7–8.7)	5.5 (3.8–7.8)	5.6 (3.8–7.3)	0.53

p Values for differences between two treatment groups by Mann–Whitney U test or Fisher’s exact test. Anti-CCP, anticyclic citrullinated protein antibodies (in serum); DAS28CRP, Disease Activity Score; s-CRP, serum C-reactive protein; VAS, visual analogue scale.

Data were collected in the DANBIO database.²² Data management and statistical analysis were done using the R software package.

RESULTS

Patient characteristics

Baseline characteristics did not differ between the treatment groups (table 1).

The 12 months’ study period was completed by 161 patients (89%), and 170 (94%) had a 12-month (ITT) visit. The most common reasons for withdrawal were patient request/non-compliance,⁸ lack of efficacy⁵ and cancer³ (figure 1).

Treatment at 12 months

Methotrexate dosage was 20 mg/week (median) in both groups. There was no difference in the number of visits, including extra visits. The cumulative dose of triamcinolone and number of joint injections did not differ between groups. Triple therapy (ie, adding sulphasalazine and hydroxychloroquine to methotrexate) was introduced in 18 patients in the adalimumab group and 27 patients in the placebo group (p=0.17) (table 2). Three patients in the adalimumab group and two patients in the placebo group were withdrawn from the study due to severe disease

activity and treated with open label biologics (etanercept (3), infliximab (1), tocilizumab (1)).

Clinical efficacy

Eighty per cent of patients in the adalimumab group and 76% of patients in the placebo group achieved the primary outcome: DAS28CRP<3.2 at 12 months (p=0.65) (table 2 and figure 2). NRI analysis gave similar results (table 2).

The decline in DAS28CRP from baseline was significantly greater in the adalimumab group throughout the study (figure 2). At 12 months, the DAS28CRP was 2.0 (1.7–5.2) in the adalimumab group versus 2.6 (1.7–4.7) in the placebo group (p=0.009).

The proportion of patients achieving remission was consistently higher for the adalimumab group than for the placebo group (figure 2). The NNT with adalimumab to achieve remission in one extra patient was 5.1–8.4 and 4.0–5.4 at 1 and 12 months, respectively, depending on remission criteria used (table 2). To allow comparison with other studies, the ACR and EULAR response rates are also shown (table 2).

Median HAQ scores decreased within the first month in both groups and remained low. Thus, after initiation of treatment, more than 55% of patients in both groups had a HAQ<0.5

Figure 1 Flow chart of Optimised treatment algorithm in Early Rheumatoid Arthritis trial; 180 patients followed for 12 months.

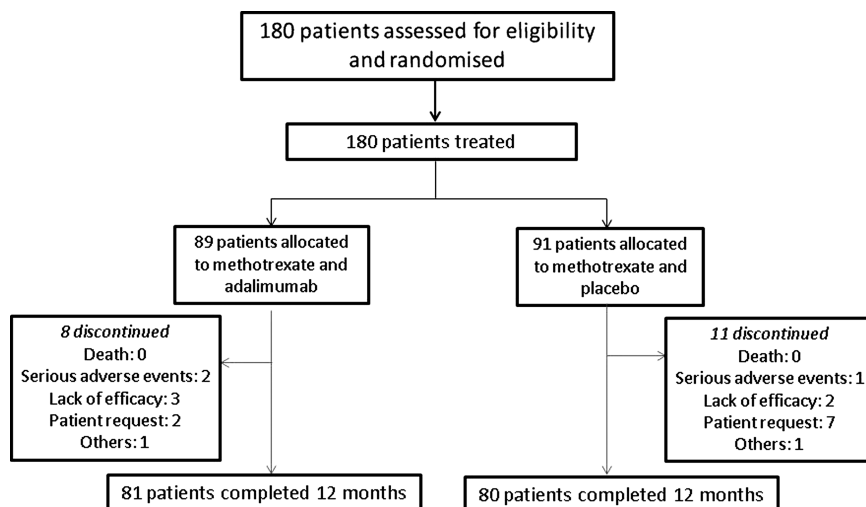


Table 2 Treatment, treatment responses and remission rates after 12 months

	Adalimumab-group	Placebo-group	p Value	NNT
Treatment				
Methotrexate dosage at 1 year	20 (7.5–20)	20 (11.5–20)	0.24	–
Methotrexate dosage at 1 year (mean(SD))	18.0 (4.1)	18.6 (3.3)	0.24	–
Number of extra visits/total visits	91/605	111/609	0.23	–
Cumulative triamcinolone dose 0–3 months (ml)	5 (1.8–13)	5.5 (2–12)	0.52	–
Cumulative triamcinolone dose at 1 year (ml)	5.4 (1.8–17.4)	7 (2–18.8)	0.08	–
Number of patients receiving intra-articular injections after baseline visit	79	74	0.63	–
Triple therapy started during the study	20%	30%	0.17	–
Open-label biologics at 1 year	3%	2%	0.98	–
Clinical efficacy after 1 year				
Clinical parameters				
Tender joint count (0–28)	0 (0–13)	0 (0–9)	0.08	–
Swollen joint count (0–28)	0 (0–6)	0 (0–3)	0.20	–
VAS patient global (0–100)	10 (0–54)	18 (0–69)	0.08	–
VAS patient pain (0–100)	7 (0–64)	20 (0–71)	0.007	–
VAS patient fatigue (0–100)	16 (0–81)	20 (0–84)	0.10	–
VAS doctor's global (0–100)	1 (0–59)	4 (0–33)	0.03	–
CRP QUICK-READ (7–161)	7 (7–21)	7 (7–44)	0.21	–
Composite disease activity scores				
DAS28CRP (1.7–8.7)	2.0 (1.7–5.2)	2.6 (1.7–4.7)	0.009	–
CDAI (0–76)	1.9 (0–27.9)	3.9 (0.1–17.2)	0.01	–
SDAI (0.7–82)	2.7 (0.7–30.4)	5.0 (0.8–20.2)	0.006	–
Treatment target				
DAS28CRP<3.2	80%	76%	0.65	–
DAS28CRP<3.2 with NRI analysis	78%	71%	0.44	–
Remission				
DAS28CRP<2.6	74%	49%	0.0008	4.0 (2.6–9.1)
CDAI≤2.8	61%	41%	0.008	5.0 (2.9–17.5)
SDAI<3.3	57%	37%	0.007	4.3 (2.6–11.0)
ACR/EULAR 28 joint remission	48%	30%	0.014	5.4 (3.1–22.1)
ACR/EULAR 40 joint remission	47%	26%	0.005	4.8 (2.9–14.5)
Response rates				
ACR20	86%	78%	0.21	–
ACR50	80%	63%	0.020	5.9 (3.3–25.8)
ACR70	65%	45%	0.012	5.1 (2.9–18.8)
EULAR good/moderate/none	82/11/7	74/20/7	0.28	–

Values are median, 5th/95th percentile ranges or % of patients. p Values for differences between two treatment groups by Mann–Whitney U test or Fisher's exact test. Number-needed-to-treat (NNT): 5/95% CIs (only calculated if $p < 0.05$). CRP, C-reactive protein (serum). Values outside the lower and upper measurement range were set at 7 and 161, DAS28CRP. Disease Activity Score, 28 joints, CRP based; CDAI, Clinical Disease Activity Index; SDAI, Simplified Disease Activity Index; VAS, Visual Analogue Scale. DMARD, disease modifying antirheumatic drug; ACR, American College of Rheumatology; EULAR, European League Against Rheumatism; NRI, non-responder imputation.

throughout the study. The decline in HAQ from baseline was significantly greater in the adalimumab group (table 3). A significant and sustained increase was observed in both groups in SF12-MCS within the first month but with no significant differences between the groups (table 3). The SF12-PCS and EQ-5D were significantly poorer in the placebo group than in the adalimumab group after 12 months (table 3).

Adverse events

SAE were reported in 14 patients in the adalimumab group and 10 patients in the placebo group, including three malignancies in the adalimumab group: small cell lung carcinoma, myelodysplastic syndrome and basocellular carcinoma and two malignancies in the placebo group: urothelial carcinoma and basocellular carcinoma. Three serious infections were observed in either group: empyema, pneumonia and bronchitis in the adalimumab group and pneumonia, bronchitis and dental abscess in the

placebo group. One suspected, but unconfirmed infectious arthritis in the adalimumab group was also observed. The remaining SAE included local subcutaneous atrophy (1), blurred vision (1), acute myocardial infarction (1), tachycardia (1) and gonarthrosis (1) in the adalimumab group and fivefold increased serum alanine aminotransferase (2), disease exacerbation (1), leucopoenia (1), polyneuropathia (1), peptic ulcer (1), coronary bypass (1), hip fracture (1) and coxarthrosis (1) in the placebo group. One patient in the placebo group, who terminated the study due to non-compliance after 6 months, died due to pneumonia 4 months later.

DISCUSSION

Although the proportion of patients who achieved a DAS28CRP<3.2 response did not differ between the two treatments (80% vs 76%, $p=0.65$), DAS28CRP was significantly

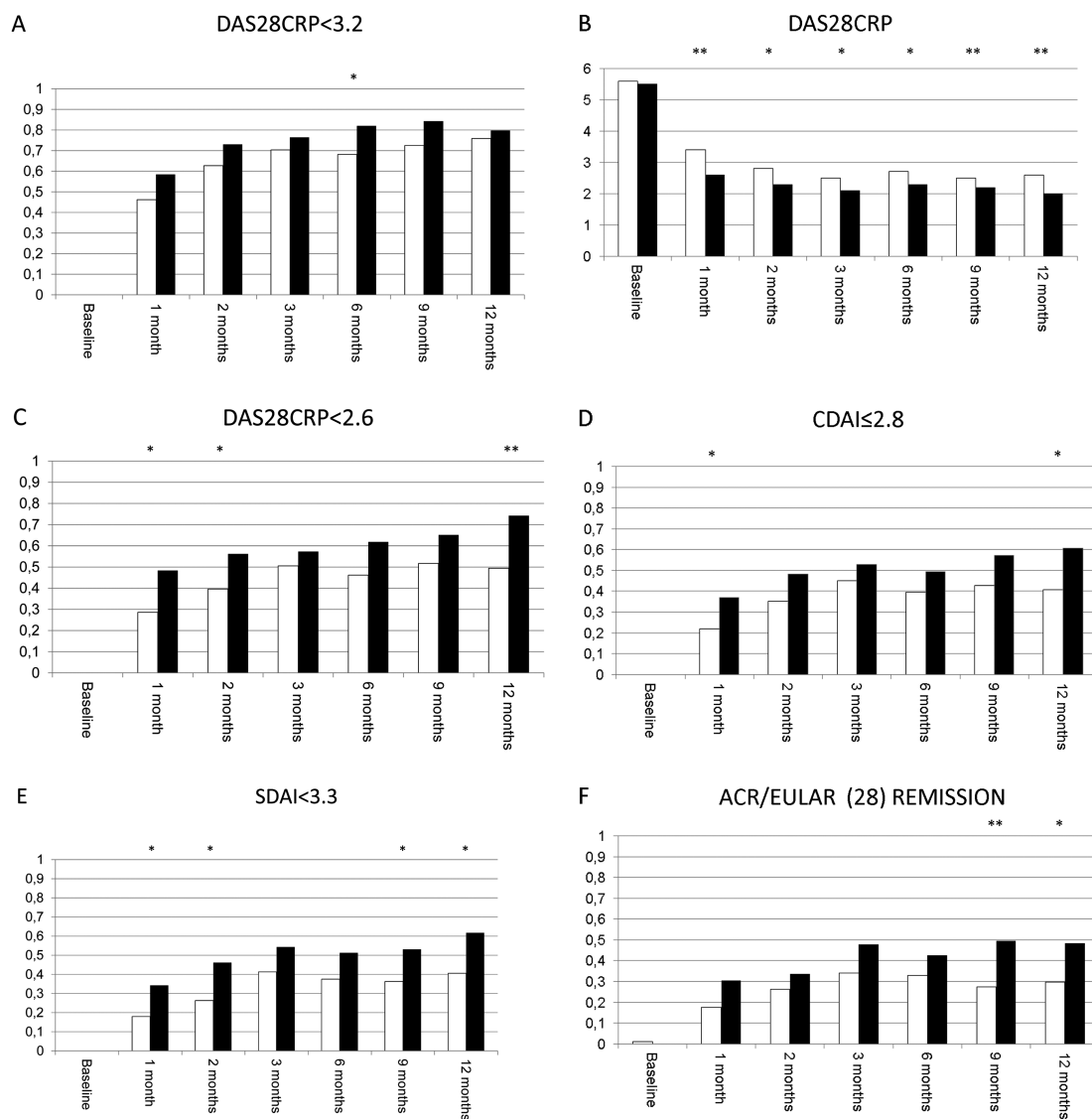


Figure 2 Black columns: adalimumab group, white columns: placebo group. DAS28CRP and the proportion of patients in each treatment group at each visit during the 12-month study achieving low disease activity and remission. (A) DAS low disease activity (DAS28CRP<3.2), (B) DAS28CRP, (C) DAS remission (DAS28CRP<2.6), (D) Clinical Disease Activity Index (CDAI) remission (CDAI≤2.8), (E) Simplified Disease Activity Index (SDAI) remission (SDAI<3.3), (F) American College of Rheumatology/European League Against Rheumatism remission (Boolean, 28 joints). **p<0.01, *p<0.05. p Values for differences between two treatment groups by Mann–Whitney U test or Fisher’s exact test.

lower in the adalimumab group throughout the study as compared with the placebo group (table 2, figure 2).

By contrast, combining adalimumab with methotrexate and intra-articular glucocorticoid injections as first-line therapy in

early RA significantly improved the remission rates. In both groups, adherence to the study protocol was high, and treatments were well tolerated with no significant differences in the use of methotrexate, intra-articular glucocorticoids or triple therapy.

Table 3 Disability and health-related quality of life at baseline and 12 months

	Adalimumab group			Placebo-group			p Value between groups	
	Baseline	12 months	0–12 months	Baseline	12 months	0–12 months	12 months	0–12 months
HAQ (0–3)	1.13 (0.17–2.58)	0.25 (0–1.44)	−0.88 (−2.46–0.13)	1.00 (0.25–2.31)	0.13 (0–1.5)	−0.63 (−1.82–0.38)	0.14	0.012
SF-12 PCS (0–100)	30.9 (13.1–50.6)	49.2 (29.9–56.6)	13.2 (−2.3–33.0)	31.7 (19.3–44.5)	43.3 (26.1–55.8)	10.6 (−11.2–22.7)	0.016	0.015
SF-12 MCS (0–100)	47.0 (28.6–60.6)	55.7 (35.8–62.6)	5.5 (−8.5–20.1)	46.7 (25.7–60.1)	54.8 (40.4–63.7)	4.3 (−9.3–27.4)	0.68	0.83
EQ-5D (0–1)	0.61 (0.17–0.80)	0.82 (0.38–1.00)	0.22 (−0.05–0.67)	0.64 (0.22–0.80)	0.78 (0.49–1.00)	0.20 (−0.06–0.56)	0.04	0.095

Values presented as medians (5th/95th percentile ranges) or % of patients. p Values for differences between two treatment groups by Mann–Whitney U test or Fisher’s exact test.

Baseline values did not differ statistically significant between groups.

DMARD, disease modifying antirheumatic drug; EQ-5D, European quality of life-5 dimensions; HAQ, Health Assessment Questionnaire; SF12 MCS, Short Form 12-item Survey V.2 Health Survey Mental Component Score; SF12 PCS, Short Form 12-item Survey V.2 Health Survey Physical Component Score.

In the adalimumab group, 74% were in DAS remission, 61% in CDAI remission, 57% in SDAI remission, and 48%/47% in ACR/EULAR Boolean (28/40 joint) remission at 12 months. Accordingly, we found significantly higher ACR50 and ACR70 response rates in the adalimumab group. Compared with the placebo group, the corresponding remission rates for the placebo group were lower, although very high compared with other studies (49%, 41%, 37% and 30%/26%, respectively). The impact of adding adalimumab was reflected in a NNT between 4.0 and 5.4 to achieve one additional case of remission after 12 months by adding adalimumab. The remission rates in the placebo group were higher than those reported in the CIMESTRA study,⁵ which may reflect an intensified methotrexate treatment (faster escalation and higher final dose) and early initiation of triple therapy²³ if treatment goal was not achieved. The possible influence of the shift in intra-articular glucocorticoid administered from betamethasone (CIMESTRA) to triamcinolone (OPERA) cannot be assessed, but a previous study indicated a longer-lasting effect of intra-articularly injected triamcinolone compared with betamethasone in juvenile arthritis.²⁴ The current OPERA study confirmed that aggressive treatment with methotrexate at an appropriate dosage (20 mg/week) combined with intra-articular glucocorticoids in any swollen joint (large or small) and early initiation of triple therapy is highly efficacious in bringing early RA patients into remission.^{25–27}

The benefit of a treat-to-target strategy in early RA including oral steroids (7.5–10 mg daily with or without higher starting dose) has been reported in several recent studies.^{28–32} In the present study, we chose a different route for the administration of glucocorticoids by using intra-articular injections, which might have greater efficacy and fewer side effects than systemically administered glucocorticoids in RA.^{33–34} In the CIMESTRA study, we demonstrated that this approach resulted in low cumulative doses of glucocorticoids and long-lasting remission in the injected joints.³⁵ In the present study, the cumulative dose corresponded to less than 1 mg prednisolone/day, and less than 5% of patients received a cumulative dose of triamcinolone corresponding to more than 2 mg prednisolone/day during the study (assuming that 40 mg of triamcinolone is equivalent to 50 mg of prednisolone).

Other studies have also reported a superior effect of early TNFi therapy in treatment-naïve patients with newly diagnosed RA.^{7–12} The PREMIER study demonstrated that adalimumab and methotrexate were superior to adalimumab or methotrexate alone, resulting in DAS28 remission in 44%, 23% and 21% of patients, respectively.⁷ The studies were traditional drug trials with rather rigid treatment regimes, for instance, not allowing systematic injection of glucocorticoids into swollen joints. This may explain, at least in part, why those studies on the one hand reported greater effects of adding TNFi, but on the other hand, lower remission rates in both groups compared with the present study. These trials did not focus on strategy, but rather on drugs. By contrast, the present study was a strategy trial, aiming to achieve a low disease activity (DAS28CRP<3.2)¹³ using a flexible treatment strategy which allowed for dosage adjustments according to current disease activity.

Three recent studies are similar to ours in relation to study design, treatment choice and outcome, although they only allowed fixed oral prednisolone up to 10 mg daily, and zero or one intra-articular injection during the study.^{36–38} The GUEPARD open design study³⁶ compared methotrexate monotherapy with methotrexate plus adalimumab for 3 months. Faster control of disease activity was achieved in the adalimumab group, but no persistent differences were observed,

probably because the study was underpowered due to difficulties in patient recruitment. The randomised, controlled OPTImal protocol for Methotrexate and Adalimumab combination therapy in early rheumatoid arthritis (OPTIMA)³⁷ and High Induction Therapy with Anti-Rheumatic Drugs trial (HIT-HARD)³⁸ studies compared methotrexate monotherapy with methotrexate plus adalimumab for the first 6 months, and found that a higher proportion of patients achieved low disease activity and remission in the combination-therapy group compared with monotherapy. However, the DAS28 remission rates after 6 months were lower in the OPTIMA (17% in monotherapy and 34% in the combination-therapy group) and HIT-HARD (30% and 48%) studies compared with our study (46% and 62%). This may reflect baseline differences in study groups with slightly higher baseline DAS28 of 6.0–6.2 in the two studies, compared with 5.6 in the present study, and differences in the presence of autoantibodies at baseline and in treatment duration. More likely, the higher remission rates in our study may reflect the consistent use of individualised, intra-articular glucocorticoid injections in the present study as part of the treat-to-target strategy. The latter may also explain why—in contrast with the OPTIMA study—we did not observe any difference between groups with respect to achieving low disease activity.

The clinical improvements were reflected in near-normalisation of HAQ, SF-12 and EQ-5D in both treatment groups, despite significantly impaired functional status and health-related quality of life at the time of study entry. Normalisation of HAQ was observed within 1 month in the majority of patients and was maintained thereafter. Compared with placebo, adalimumab caused a marked and clinically meaningful difference in physical function, as measured by the HAQ, whereas the changes in SF-12 PCS and EQ-5D were hardly clinically significant. There was no consistent effect of adalimumab on SF-12 MCS. This may reflect the fact that SF-12 MCS has low sensitivity to change.¹⁸

It has been suggested that the favourable results in the CIMESTRA study could, in part, be accounted for by the frequent study visits (15 in 1 year). In the present study, patients were seen monthly for the first 3 months, and then every third month. This is close to routine care in early RA clinics, and is in accordance with recommendations of the treat-to-target international task force.² There was no difference in the number of extra visits between the groups (table 2). The safety profiles were good, and the treatments were well tolerated in this early patient population, with limited comorbidity.

The study has strengths and weaknesses. The double-blinded, placebo-controlled, prospective design is a significant strength. Furthermore, although many well performed and large randomised clinical trials have been published during the past two decades, investigator-initiated trials are scarce, and the rigid trial regimens are seldom applicable to clinical practice. The high completion rate in our study adds to the statistical strength of the study. With today's knowledge, remission may have been selected as the primary outcome. However, when the trial was designed, low disease activity was considered a strict target.

This study is the first DMARD study in patients with early RA where NSAID was prohibited. This was decided because NSAID could potentially blur the recognition of swollen joints. Patients with persistently tender joints and elevated global pain scores due to chronic pain comorbidities (eg, osteoarthritis and fibromyalgia) were eligible for the study and could therefore theoretically mask response rates.³⁹ However, pain scores decreased dramatically in both groups, indicating that this was not a major issue in this population.

In conclusion, the proportion of patients achieving the predefined treatment target at DAS28CRP<3.2 did not differ between the two groups. However, combining adalimumab with an oral methotrexate step-up strategy and intra-articular glucocorticoid injections improved DAS28CRP, physical function, quality of life and remission rates significantly throughout the study period in this investigator-initiated protocol on DMARD-naïve patients with early RA.

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Contributors The study was designed by the principal investigator in collaboration with other investigators in the OPERA Study Group and all data were collected by the Study Group. All the investigators contributed to the design, analysis and writing of the report. KHP and KSP were the principal investigators and KHP the study centre coordinator. The administrative board of the study consisted of KHP, ML, PJ, TL JP, HL, JSJ, MØ and KSP.

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