

## CLINICAL SCIENCE

# Certolizumab pegol, abatacept, tocilizumab or active conventional treatment in early rheumatoid arthritis: 48-week clinical and radiographic results of the investigator-initiated randomised controlled NORD-STAR trial

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## ABSTRACT

**Background** The optimal first-line treatment in early rheumatoid arthritis (RA) is debated. We compared clinical and radiographic outcomes of active conventional therapy with each of three biological treatments with different modes of action.

**Methods** Investigator-initiated, randomised, blinded-assessor study. Patients with treatment-naïve early RA with moderate–severe disease activity were randomised 1:1:1:1 to methotrexate combined with (1) active conventional therapy: oral prednisolone (tapered quickly, discontinued at week 36) or sulfasalazine, hydroxychloroquine and intra-articular glucocorticoid injections in swollen joints; (2) certolizumab pegol; (3) abatacept or (4) tocilizumab. Coprimary endpoints were week 48 Clinical Disease Activity Index (CDAI) remission (CDAI  $\leq 2.8$ ) and change in radiographic van der Heijde-modified Sharp Score, estimated using logistic regression and analysis of covariance, adjusted for sex, anticitrullinated protein antibody status and country. Bonferroni's and Dunnett's procedures adjusted for multiple testing (significance level: 0.025).

**Results** Eight hundred and twelve patients were randomised. Adjusted CDAI remission rates at week 48 were: 59.3% (abatacept), 52.3% (certolizumab), 51.9% (tocilizumab) and 39.2% (active conventional therapy). Compared with active conventional therapy, CDAI remission rates were significantly higher for abatacept (adjusted difference +20.1%,  $p < 0.001$ ) and certolizumab (+13.1%,  $p = 0.021$ ), but not for tocilizumab (+12.7%,  $p = 0.030$ ). Key secondary clinical outcomes were consistently better in biological groups. Radiographic progression was low, without group differences.

## WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Early treatment is associated with improved outcome in patients with recently diagnosed rheumatoid arthritis (RA), but the optimal first-line treatment is debated.

## WHAT THIS STUDY ADDS

⇒ For the first time, three biologics with different modes of action, all in combination with methotrexate, were compared head-to-head against active conventional antirheumatic therapy with bridging glucocorticoids in a randomised clinical trial in patients with early RA.  
⇒ Compared with active conventional therapy, clinical remission rates were superior for abatacept and certolizumab pegol, but not for tocilizumab.  
⇒ Radiographic progression was low and similar between treatments.

## HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The findings should be considered in the future management of patients with newly diagnosed RA.

The proportions of patients with serious adverse events were abatacept, 8.3%; certolizumab, 12.4%; tocilizumab, 9.2%; and active conventional therapy, 10.7%.

**Conclusions** Compared with active conventional therapy, clinical remission rates were superior for abatacept and certolizumab pegol, but not for tocilizumab. Radiographic progression was low and similar between treatments.

**Trial registration number** NCT01491815.

## INTRODUCTION

Rheumatoid arthritis (RA) is a chronic inflammatory joint disease which causes pain, fatigue, functional impairment and frequently progressive joint destruction.<sup>1</sup> Early treatment is associated with improved outcome.<sup>2</sup> The optimal first-line treatment of patients with early RA is debated. Several trials have shown superior outcomes in treatment-naïve patients treated with biological disease-modifying antirheumatic drugs (bDMARDs) in combination with methotrexate (MTX) compared with MTX monotherapy.<sup>3–5</sup> Yet, both US and European recommendations advocate conventional synthetic disease-modifying drugs (csDMARDs) as the first-line therapy, with MTX as the anchor drug.<sup>6,7</sup> This approach is supported by evidence suggesting that short-term addition of glucocorticoids to MTX (and/or other csDMARDs) yields results comparable with those achieved by bDMARDs.<sup>8,9</sup> Despite various modes of action, bDMARDs are perceived as having overall similar efficacy.<sup>6,7</sup> However, this is mainly based on indirect comparisons since head-to-head trials in early RA are few.<sup>10–12</sup>

Therefore, an investigator-initiated six-country collaboration was established to perform a randomised controlled trial, the Nordic Rheumatic Diseases Strategy Trials and Registries (NORD-STAR) study, to compare the benefits and harms of optimised conventional therapy ('active conventional therapy'), that is, MTX combined with either oral glucocorticoids or intra-articular glucocorticoids and other csDMARDs and three different biological therapies in combination with MTX (tumor-necrosis factor inhibitor (certolizumab pegol), T-cell costimulation modulator (abatacept) and interleukin-6 inhibitor (tocilizumab)). Twenty-four week clinical results from this study have been published, showing high remission rates in all four arms, and active conventional therapy being non-inferior to certolizumab pegol and tocilizumab but not to abatacept.<sup>13</sup> A comparison of the ability to halt structural damage progression, which is key to the long-term joint status and disability experienced by the patient,<sup>14,15</sup> was not performed at 24 weeks, since the primary radiographic endpoint was at 48 weeks. Furthermore, clinical results at 48 weeks are less influenced by initial glucocorticoid bridging therapy. Thus, interdrug differences in efficacy and safety may have become more manifest at week 48 and thereby more relevant to clinical practice.

We aimed to perform a head-to-head comparison of the clinical efficacy and radiographic structural damage progression up to week 48 of active conventional therapy and each of three bDMARDs with different modes of action in combination with MTX in patients with treatment-naïve RA.

## METHODS

### Study design

The design of this investigator-initiated, multicentre, randomised, open-label, blinded-assessor trial (<https://clinicaltrials.gov/ct2/show/NCT01491815>) has been published previously.<sup>16</sup> Patients were randomised to one of four different treatment arms aiming at achieving remission. This report describes the analyses regarding the initial 48 weeks of the trial, including two coprimary (one clinical and one radiographic) outcomes and

secondary clinical, radiographic and safety outcomes. The trial was designed, overseen and analysed by a steering committee of academic investigators. The reporting follows the Consolidated Standards of Reporting Trials statements.<sup>17,18</sup> Patient representatives were not involved in the design and conduct of this research.

### Patients

Patients with early RA according to the American College of Rheumatology (ACR) and European Alliance of Associations for Rheumatology (EULAR) 2010 classification criteria were included (table 1).<sup>19</sup> Key inclusion criteria were age  $\geq 18$  years; symptom duration of  $< 24$  months; moderate to severe disease activity with Disease Activity Score (28 joints) (DAS28) score of  $> 3.2$  (Disease Activity Score calculated from 28 swollen and tender joint counts, Patient Global Score and C-reactive protein (CRP)),  $\geq 2$  (of 66) swollen and  $\geq 2$  (of 68) tender joints, and rheumatoid factor or anticitrullinated protein antibody positivity (ACPA) or CRP of  $\geq 10$  mg/L. The key exclusion criterion was previous treatment with disease-modifying antirheumatic drug (DMARD) (see online supplemental appendix for details).

### Randomisation and procedures

Randomisation was done 1:1:1:1, stratified by country, gender and ACPA status (see online supplemental appendix for details).

All patients started MTX on day 1 (escalated to 25 mg/week within 4 weeks) with folic acid supplementation (minimum 5 mg/week) combined with: Arm 1 (Active conventional therapy): either oral prednisolone (tapered from 20 mg/day to 5 mg/day in 9 weeks and discontinuation after 9 months (arm 1A) or enterotablets sulphasalazine (2 g/day), hydroxychloroquine (35 mg/kg/week or 200 mg/day) and intra-articular triamcinolone hexacetonide injection (or equivalent) in all swollen joints at each visit (maximally 4 joints and 80 mg/visit) (arm 1B); arm 2 (certolizumab pegol): 200 mg EOW SC (400 mg at 0, 2 and 4 weeks); arm 3 (abatacept): 125 mg/week subcutaneously; arm 4 (tocilizumab): 8 mg/kg/4 weeks intravenously or 162 mg/week subcutaneously. In arms 2–4, intra-articular glucocorticoid injections were allowed on demand up to week 12; thereafter, up to 40 mg were allowed every 12 weeks. In all arms, intraarticular glucocorticoids were prohibited in weeks 20–24 and 44–48 to minimise its influence on week 24/48 outcomes. Subjects were, as per investigator judgement, allowed to de-escalate MTX due to toxicity/intolerability, and to subsequently re-escalate up to 20 mg/week. In case of intolerability to oral MTX, subcutaneous MTX could be used. Non-steroidal anti-inflammatory drugs were allowed throughout the study.

The treatment strategy in arm one was predefined based on national recommendations for conventional RA therapy in the individual countries: arm 1A: Sweden, Norway, Iceland and Netherlands, and arm 1B: Denmark and Finland. Clinical examination included joint assessments for swelling and tenderness by independent blinded assessors. Patient reported outcomes included visual analogue scales for pain and global assessment and physical function (Health Assessment Questionnaire). These and blood samples (including CRP) were acquired at weeks 0, 4, 8, 12, 16, 24, 32, 40 and 48 (table 1).<sup>16</sup> Clinical Disease Activity Index (CDAI) was calculated as the sum of swollen joint count (0–28), tender joint count (0–28), Patient's Global Score of Disease Activity (0–10) and Investigator's Global Score of Disease Activity (0–10).<sup>20</sup>

Conventional radiographs of hands and feet were obtained at screening, week 24 and 48, and analysed for bone erosion and

**Table 1** Demographics and patient characteristics at baseline (ITT population).

Parameter	Active conventional therapy (n=200)	Certolizumab pegol and MTX (n=203)	Abatacept and MTX (n=204)	Tocilizumab and MTX (n=188)*
Demographics				
Age (years)	55 (15)	55 (15)	55 (14)	52 (15)
Women, n (%)	139 (70)	139 (69)	140 (69)	129 (69)
Symptom duration (days)	195 (167)	203 (166)	212 (168)	208 (155)
Time since diagnosis (days)	13 (21)	12 (17)	16 (34)	16 (33)
Anticitrullinated peptide antibody positive, n (%)	163 (82)	166 (82)	169 (83)	153 (82)
Rheumatoid factor positive, n (%)	151 (76)	149 (73)	159 (78)	135 (72)
Baseline characteristics, clinical				
Clinical Disease Activity Index	28.7 (12.1)	27.9 (12.4)	28.6 (11.3)	26.6 (11.7)
Disease Activity Score, 28 Joints, CRP-based	5.1 (1.1)	5 (1.1)	5.1 (1)	4.9 (1)
Tender joint count, 68 joints	17 (11)	15 (10)	16 (11)	15 (10)
Swollen joint count, 66 joints	11 (7)	11 (8)	11 (7)	10 (6)
Patient's Global Assessment of Disease Activity (mm)	56.7 (23.2)	56.6 (23.7)	60.4 (23.6)	57.4 (22.6)
Physician's Global Assessment of Disease Activity (0–100 mm)	48.8 (19.2)	49.3 (19.2)	51.7 (18.7)	49.7 (18.1)
Patient's Assessment of Pain (0–100 mm)	56 (24.2)	55.7 (24.7)	59.3 (24.2)	55.3 (23)
HAQ score (0–3)	1.1 (0.6)	1 (0.6)	1.1 (0.6)	1.1 (0.5)
Baseline characteristics, radiography				
Radiographic score, total (0–448)	6.3 (8.2)	5.9 (7.6)	5.8 (9.8)	4.2 (6.7)
Radiographic score, total (0–448), median (IQR)	4 (1.0–8.5)	3 (1–8)	3 (1–6)	2 (0.5–5.0)
Radiographic score, erosion (0–280)	2.96 (4.45)	2.97 (4.58)	2.43 (4.64)	2.03 (4.33)
Radiographic score, erosion (0–280), median (IQR)	1 (0–4)	1 (0–4)	1 (0–2.5)	0.5 (0–2)
Radiographic score, JSN (0–168)	3.36 (4.49)	2.96 (3.64)	3.39 (5.85)	2.2 (3.04)
Radiographic score, JSN (0–168), median (IQR)	2 (0–5)	2 (0–4.25)	2 (0–4)	1 (0–3)

Values are mean (SD), if not otherwise indicated.  
 Radiographic status: as assessed by van der Heijde-modified Sharp Score.  
 \*Seventeen Finnish patients randomised to arm 4 (Tocilizumab+MTX), but not receiving it due to unavailability, are not included. They were excluded from the ITT population to allow a fair analysis of the efficacy of Tocilizumab. Robustness analyses showed comparable results.  
 CRP, C reactive protein; HAQ, Health Assessment Questionnaire; ITT, intention to treat; JSN, joint space narrowing; MTX, methotrexate; n, number of patients.

joint space narrowing (JSN) using the van der Heijde-modified Sharp Score (vdHSS), with known chronology, by two experienced, independent readers, blinded to all clinical data.<sup>21</sup> A total vdHSS (range 0–448) was calculated by adding erosion (0–280) and JSN (0–168) scores. The average of readers' scores was used. In case of reader discrepancies in mean change in the total vdHSS from baseline to week 48 ( $\Delta$ total-vdHSSw0–w48) of  $\geq 2$ , a final score was reached by reader consensus.

## Outcomes

The two coprimary outcomes were clinical remission at week 48 (primary clinical outcome, defined as remission (CDAI  $\leq 2.8$ ); dichotomous outcome)<sup>20</sup> and the change in radiographic score from baseline to week 48 ( $\Delta$ total-vdHSSw0–w48; primary radiographic outcome, continuous outcome)<sup>21</sup> (online supplemental file 2, statistical analysis plan (SAP)). The coprimary outcomes were CDAI remission at week 24 and the aforementioned  $\Delta$ total-vdHSSw0–w48. The 24-week clinical results, but no radiographic results, have been published previously.<sup>13</sup> For the 48 week analysis, the CDAI remission rate at week 48 was added as a coprimary outcome, prior to any analyses (online supplemental file 2, SAP).

Key secondary clinical outcomes were ACR/EULAR Boolean remission, DAS28 remission, Simplified Disease Activity Index remission and EULAR good response at week 48.<sup>20 22 23</sup> Key secondary radiographic outcomes were no radiographic progression ( $\Delta$ vdHSS from baseline to 48 weeks  $< 1$ ), changes from baseline to week 48 in vdHSS erosion scores and vdHSS JSN score and changes from baseline to week 24 and from week 24

to week 48 in total vdHSS. Other secondary clinical and radiographic outcomes are presented in online supplemental file 2 (SAP) and online supplemental appendix table S1–S7.

Safety outcomes were the numbers and percentages of patients with serious and non-serious adverse events for each treatment arm. Predefined adverse events of special interest are defined in table 2. All safety events were MedDRA V.22.0 coded.

## Statistical analysis

Assuming remission rates in active conventional therapy, certolizumab pegol, abatacept and tocilizumab arms of 12%, 22%, 22% and 26%, respectively, 724–832 patients had to be randomised to reach 85%–90% power for rejecting the null hypothesis of no treatment difference<sup>3 24–28</sup> (see Hetland *et al*<sup>13</sup> for details).

This part of the trial was designed to establish the superiority of at least one of the biological treatments compared with active conventional therapy at 48 weeks on (1) achieving CDAI remission and (2) preventing progression in the radiographic van der Heijde-modified Sharp Score. Thus, there were six separate null hypotheses to be tested. To adjust for multiplicity, each of the two outcome families were tested against an overall significance level of 0.025. Superiority was claimed if any of the six hypotheses were rejected on the 0.025 level using adjusted p values according to Dunnett's method when having a common comparator.<sup>29</sup>

The primary analysis population was the intention-to-treat population, defined as all randomised patients except 17 Finnish patients, for whom allocated treatment (tocilizumab) was not available (see online supplemental file 2) (SAP)). Primary and

**Table 2** Adverse events in the safety population\*

Parameters†	Active conventional therapy (n=197)	Certolizumab pegol and MTX (n=202)	Abatacept and MTX (n=204)	Tocilizumab and MTX (n=184)
Summary of adverse events				
Adverse events	(784) 174 (88.3%)	(736)181 (89.6%)	(735) 175 (85.8%)	(886) 178 (96.7%)
Serious adverse events	(23) 21 (10.7%)	(28) 25 (12.4%)	(21) 17 (8.3%)	(20) 17 (9.2%)
Deaths		(2) 2 (1.0%)‡		
Adverse events of special interest§				
Infections	(153) 93 (47.2%)	(157) 94 (46.5%)	(181) 99 (48.5%)	(201) 107 (58.2%)
Cardiovascular disease	(4) 4 (2%)	(9) 8 (4%)	(16)12 (5.9%)	(7) 7 (3.8%)
Cataract	(6) 3 (1.5%)		(3) 2 (1%)	(1) 1 (0.5%)
Deep vein thrombosis		(1) 1 (0.5%)		
Demyelinating disease		(1) 1 (0.5%)		
Diabetes mellitus	(3) 2 (1%)			
Herpes zoster	(5) 5 (2.5%)	(3) 2 (1%)	(1) 1 (0.5%)	(1) 1 (0.5%)
Malignancy	(3) 3 (1.5%)	(5) 5 (2.5%)	(3) 3 (1.5%)	(6) 6 (3.3%)
Osteoporosis	(3) 3 (1.5%)	(3) 3 (1.5%)		(1) 1 (0.5%)
Weight gain	(3) 3 (1.5%)		(1) 1 (0.5%)	(2) 2 (1.1%)
Early terminations due to lack of efficacy/adverse events	22 (11.1%)/2 (1.0%)	7 (3.5%)/16 (7.9%)	7 (3.4%)/5 (2.4%)	1 (0.5%)/20 (10.8%)

Values are (number of events), number of patients (percentage of patients in that arm who experienced at least one event).  
 \*Adverse events are summarised by the safety population and by actual treatment (not as randomised). Thus, the 17 Finnish patients randomised to arm 4 (tocilizumab) but not receiving it due to unavailability are not included.  
 †(Events) number of patients (percentage of patients in that arm). Patients could have more than one category of events.  
 ‡Patient 1: sudden death in a woman in her 70s. A lump in the breast was discovered at the screening visit; later, breast cancer was diagnosed. She terminated early in the trial on study approximately on day 40, had mastectomy 5 days later and died suddenly approximately 9 weeks later. The events were assessed as not related to the study drug by the investigator. Patient 2: This patient had dyspnoea as an adverse event that started just before the week 24 visit. She was hospitalised on approximately day 200 due to 'severe lung infection, bilateral pulmonary infiltrates, respiratory insufficiency, suspicion of interstitial pneumonitis, admitted to intensive department with large oxygen requirement', and she died approximately 2 weeks thereafter. The event was assessed as probably related to study drug by the investigator.  
 §There were no events coded as tuberculosis. Osteoporosis events were reported shortly after baseline, for example, based on baseline dual-energy x-ray absorptiometry (DXA) scan.  
 MTX, methotrexate.

secondary dichotomous outcomes were analysed using a logistic regression model, adjusted for stratification factors in the randomisation (sex, ACPA status and country). We imputed missing remission status with worst case (non-remission).

The primary and other continuous radiographic outcomes were analysed using analysis of covariance, adjusted for baseline score and the stratification factors in the randomisation. Missing data were imputed in a hierarchical way.

Other continuous secondary outcomes were analysed using generalised linear mixed gamma (CRP), negative binomial (joint counts) or normal models (other), all with random intercept adjusted for baseline characteristics and value.

One author (ICO) performed analyses; details are found in online supplemental file 2 (SAP).

The funding sources had no role in study design, collection, analysis and interpretation of data; in the writing of the report; or in the decision to submit for publication.

## RESULTS

Nine hundred and three patients were assessed for eligibility at 29 sites from 3 December 2012 to 11 December 2018, whereof 812 underwent randomisation and 625 completed week 48 visit (last patient on 12 November 2019; online supplemental figure S1, patient disposition). Patient characteristics were well balanced (table 1). The patients (68.8% women, 81.9% ACPA positive, mean age 54.3 years) had early disease, with mean time since diagnosis of 14 days and mean symptom duration of 204 days.

The primary clinical outcome, the adjusted CDAI remission rates at week 48, were 39.2% for active conventional therapy, 59.3% for abatacept, 52.3% for certolizumab pegol and 51.9%

for tocilizumab (table 3 and figure 1A). The null hypotheses were formally rejected for active conventional therapy versus abatacept (adjusted difference +20.1%, adjusted  $p < 0.001$ ) and active conventional therapy versus certolizumab pegol (+13.1%,  $p = 0.021$ ), but not for active conventional therapy versus tocilizumab (+12.7%,  $p = 0.030$ ), given that the cut-off for statistical significance was 0.025. As shown in figure 2A, adjusted CDAI remission rates over time in the active conventional therapy arm after week 24 gradually separated from the three bDMARD arms, with no clear and consistent separation between bDMARD arms.

The primary radiographic outcome, the adjusted estimated  $\Delta$ total-vdHSSw0–w48, was 0.45 for active conventional therapy, 0.62 for abatacept, 0.47 for certolizumab pegol and 0.50 for tocilizumab, that is, consistently low (figure 1B). No statistically significant differences in  $\Delta$ total-vdHSSw0–w48 were found between groups (table 3). Figure 2B presents a cumulative probability plot of the radiographic progression.

Key secondary clinical outcomes were consistently numerically better in bDMARD groups compared with active conventional therapy for all remission criteria, with the abatacept group being numerically the best (table 3). All key secondary radiographic outcomes were comparable across treatment groups (table 3).

Results of other secondary clinical and radiographic outcomes can be found in table 3 and online supplemental tables S1–S7. The course over time of selected outcomes is depicted in online supplemental figures S2–S14.

The smallest detectable difference (SDC) in  $\Delta$ total-vdHSSw0–w48 was 1.43. The proportion of patients showing progression above SDC ( $\Delta$ total-vdHSSw0–w48 > SDC), reflecting progression above measurement error, in active conventional therapy,

**Table 3** Primary and secondary outcomes at week 48 (ITT population)

	Active conventional therapy (n=200)	Certolizumab pegol and MTX (n=203)	ABA and MTX (n=204)	Tocilizumab and MTX (n=188)*
Estimated adjusted outcome (ITT population)†				
<b>Coprimary outcomes</b>				
CDAI remission, week 48	39.2% (32.5 to 45.9)	52.3% (45.5 to 59.1)	59.3% (52.6 to 66)	51.9% (44.9 to 59.0)
Radiographic progression, total weeks 0–48	0.45 (0.31 to 0.59)	0.47 (0.33 to 0.61)	0.62 (0.48 to 0.76)	0.5 (0.36 to 0.64)
<b>Key secondary outcomes</b>				
ACR/EULAR Boolean remission, week 48	31.6% (25.3 to 38.0)	46.3% (39.5 to 53.1)	51.0% (44.2 to 57.8)	44.6% (37.6 to 51.6)
DAS28 remission, week 48	53.7% (46.9 to 60.6)	66.6% (60.1 to 73.0)	71.1% (65 to 77.3)	68.2% (61.6 to 74.7)
SDAI remission, week 48	38.1% (31.5 to 44.8)	52.8% (45.9 to 59.6)	57.8% (51.1 to 64.6)	53.5% (46.5 to 60.6)
EULAR good response, week 48	66.4% (59.9 to 72.9)	74.6% (68.7 to 80.6)	77.7% (72.0 to 83.4)	69.3% (62.8 to 75.9)
Radiographic progression, total $\leq 0.5$ , weeks 0–48	78.0% (72.3 to 83.8)	81.3% (75.9 to 86.7)	74.5% (68.5 to 80.5)	80.3% (74.6 to 86.0)
Radiographic progression, erosion, weeks 0–48	0.31 (0.21 to 0.4)	0.33 (0.23 to 0.42)	0.41 (0.31 to 0.5)	0.35 (0.25 to 0.45)
Radiographic progression, JSN, weeks 0–48	0.14 (0.05 to 0.23)	0.14 (0.05 to 0.23)	0.22 (0.13 to 0.31)	0.15 (0.06 to 0.24)
Estimated adjusted treatment difference (ITT population)†‡				
<b>Coprimary outcomes</b>				
CDAI remission, week 48	Reference	13.1% (3.5 to 22.6)§	20.1% (10.6 to 29.5)¶	12.7% (3 to 22.5)
$\Delta$ vdHSS total, weeks 0–48	Reference	0.02 (–0.17 to 0.22)	0.17 (–0.02 to 0.37)	0.05 (–0.15 to 0.25)
<b>Key secondary outcomes</b>				
ACR/EULAR Boolean remission, week 48	Reference	14.7% (5.4 to 23.9)	19.4% (10.1 to 28.7)	13% (3.5 to 22.4)
DAS28 remission, week 48	Reference	12.9% (3.5 to 22.2)	17.4% (8.2 to 26.6)	14.4% (5 to 23.9)
SDAI remission, week 48	Reference	14.6% (5.1 to 24.1)	19.7% (10.2 to 29.1)	15.4% (5.7 to 25.1)
EULAR good response, week 48	Reference	8.2% (–0.6 to 17.1)	11.3% (2.7 to 20.0)	2.9% (–6.3 to 12.2)
Radiographic progression, total progression $\leq 0.5$ , weeks 0–48	Reference	–3.3% (–11.1 to 4.6)	3.5% (–4.7 to 11.8)	–2.2% (–10.3 to 5.9)
Radiographic progression, erosion, weeks 0–48	Reference	0.02 (–0.12 to 0.16)	0.1 (–0.04 to 0.24)	0.04 (–0.1 to 0.19)
Radiographic progression, JSN, weeks 0–48	Reference	0 (–0.13 to 0.13)	0.08 (–0.05 to 0.21)	0.01 (–0.12 to 0.14)
<b>Secondary clinical outcomes</b>				
CDAI low disease activity, week 48	Reference	6.2% (–2.5 to 14.9)	11.3% (2.9 to 19.7)	3.1% (–5.8 to 12.1)
DAS28 low disease activity, week 48	Reference	8.7% (–0.1 to 17.5)	13.8% (5.3 to 22.3)	7.6% (–1.4 to 16.5)
ACR20 response, week 48	Reference	1.3% (–7.5 to 10.0)	8.3% (0 to 16.7)	0.9% (–8 to 9.9)
ACR50 response, week 48	Reference	9.4% (0.2 to 18.5)	13.4% (4.5 to 22.4)	3.4% (–6.2 to 13.0)
ACR70 response, week 48	Reference	14.5% (4.9 to 24.1)	13.7% (4.1 to 23.3)	9.1% (–0.8 to 18.9)
DAS28, week 48	Reference	–0.34 (–0.54 to –0.15)	–0.33 (–0.52 to –0.14)	–0.51 (–0.71 to –0.31)
CDAI, week 48	Reference	–1.41 (–2.78 to –0.03)	–1.93 (–3.28 to –0.58)	–1.75 (–3.16 to –0.33)
SDAI, week 48	Reference	–1.66 (–3.08 to –0.24)	–2.01 (–3.41 to –0.62)	–2.03 (–3.49 to –0.57)
Patient's Global Assessment of Disease Activity, 0–100 mm, week 48	Reference	–4.29 (–8.45 to –0.12)	–4.95 (–9.05 to –0.84)	–4.2 (–8.48 to 0.08)
Physician's Global Assessment of Disease Activity, 0–100 mm, week 48	Reference	–3.98 (–6.38 to –1.57)	–4.95 (–7.31 to –2.59)	–4.76 (–7.23 to –2.29)
Patient's Assessment of Pain, 0–100 mm, week 48	Reference	–5.41 (–9.41 to –1.41)	–6.03 (–9.98 to –2.09)	–5.95 (–10.07 to –1.82)
HAQ score, week 48	Reference	–0.03 (–0.11 to 0.04)	–0.04 (–0.11 to 0.04)	–0.08 (–0.16 to 0)
Serum C reactive protein, week 48	Reference	–1.93 (–2.74 to –1.12)	–0.78 (–1.67 to 0.1)	–2.96 (–3.72 to –2.21)
Erythrocyte sedimentation rate, week 48	Reference	–2.24 (–4.51 to 0.02)	–0.65 (–3.01 to 1.71)	–10.47 (–12.32 to –8.62)

Results are based on the ITT population; 17 Finnish patients allocated to tocilizumab and MTX group excluded.

Radiographic progression: as assessed by the vdHSS.

\*Since they could not receive tocilizumab because the drug was not available in the Finnish part of the study.

†Clinical variables: For dichotomous variables, values are estimated adjusted marginal difference in proportions against active conventional therapy with 95% confidence limits. Confidence limits are calculated from the logistic regression model by the delta method. Missing data are imputed using worst outcome (non-responder imputation). For continuous variables, values are adjusted marginal differences at 48 weeks with 95% confidence limits using longitudinal mixed models.

‡Radiographic scores, values are estimated adjusted marginal mean change from baseline or estimated difference against active conventional therapy with 95% confidence limits from the ANCOVA model. Missing data are imputed using interpolation or extrapolation.

§Superiority of bDMARD compared with active conventional therapy was demonstrated;  $p=0.021$

¶Superiority of bDMARD compared with active conventional therapy was demonstrated;  $p<0.001$ .

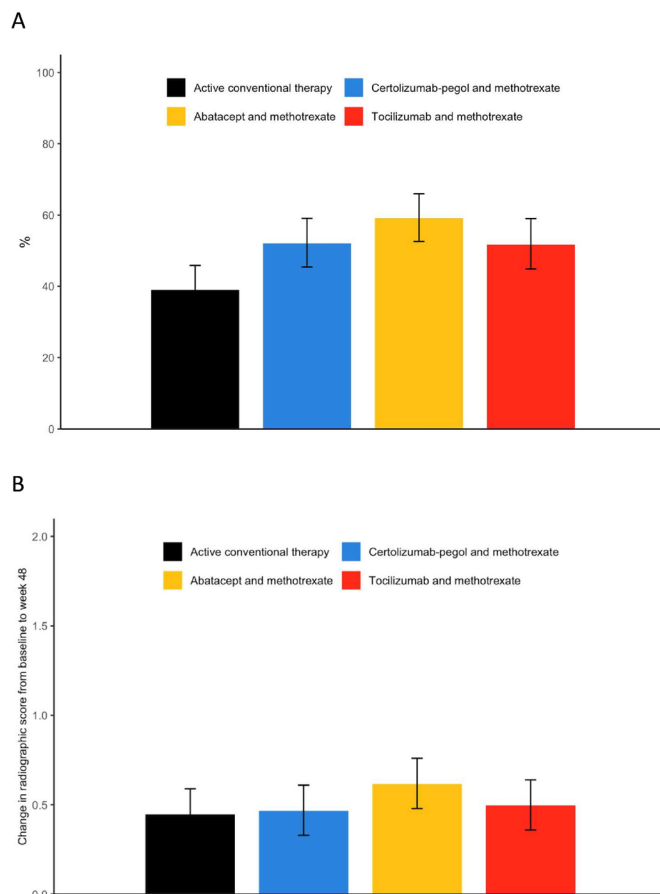
ABA, abatacept; ACR, American College of Rheumatology; ANCOVA, analysis of covariance; bDMARD, biological disease-modifying antirheumatic drug; CDAI, Clinical Disease Activity Index; DAS28, Disease Activity Score (28 joints, four variables, C reactive protein); EULAR, European Alliance of Associations for Rheumatology; ITT, intention to treat; JSN, joint space narrowing; MTX, methotrexate; n, number of patients; SDAI, Simplified Disease Activity Index; vdHSS, van der Heijde-modified Sharp Score.

abatacept, certolizumab pegol and tocilizumab groups were similar: 14.5%, 16.2%, 12.8% and 13.3%, respectively. Proportions of patients showing rapid radiographic progression ( $\Delta$ total-vdHSSw0–w48 $>5$ ) were 0%, 1%, 0% and 0%, respectively.

Results of prespecified robustness analyses of the primary and key secondary efficacy outcomes were consistent with those of the primary analyses (online supplemental tables S8–S23). Corticosteroid use was mandatory in arm 1. In arm 1A, prednisolone was reduced from 20 mg to 5 mg in 9 weeks, was stable (5 mg)

through week 32, and thereafter reduced and stopped at week 36.

In the certolizumab pegol, abatacept and tocilizumab arms, the cumulative doses of intra-articular triamcinolone hexacetonide equivalents from week 0 to week 48 were median 18 (0–49) mg, median 20 (IQR 0–60) mg and median 0 (IQR 0–40) mg, respectively, while it was median 70 (IQR 50–103) mg in arm 1B and median 0 (IQR 0–18 mg) in arm 1A (arm 1A received oral prednisolone; see previous discussion). The median cumulative dose



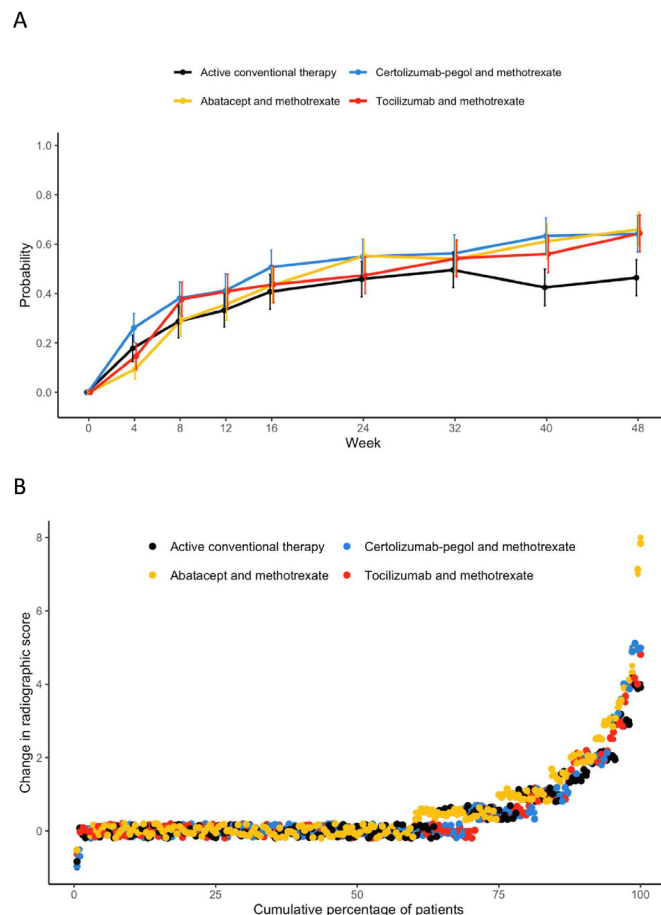
**Figure 1** Plots of the co-primary outcomes: (A) clinical remission at week 48 (adjusted Clinical Disease Activity Index remission rates at week 48) and (B) radiographic progression from baseline to week 48 (adjusted change in van der Heijde-modified total Sharp Score from baseline to week 48) for the four different treatment arms. Ninety-five per cent CIs are shown.

of intra-articular triamcinolone hexacetonide corresponded to a daily dose of 0.2 mg prednisolone in arm 1B and less than 0.1 mg in arm 1A and in the bDMARD arms (assuming 40 mg triamcinolone hexacetonide is equivalent to 50 mg prednisolone).

When split into weeks 1–24 versus weeks 25–48, doses were as follows: in arm 1B, the cumulative dose of intra-articular triamcinolone hexacetonide from week 1 to week 24 was a median of 66 (IQR 40–94) mg, while that for weeks 25–48 was only a median of 0 (IQR 0–10 mg). In arm 1A, in which oral prednisolone was administered (see previous discussion), the cumulative dose of intra-articular triamcinolone hexacetonide from week 1 to week 24 was a median of 0 (IQR 0–6) mg, while that for weeks 25–48 was a median of 0 (IQR 0–0 mg).

In the certolizumab-pegol, abatacept and tocilizumab arms, the cumulative doses of intra-articular triamcinolone hexacetonide from week 0 to week 24 were median 12 (IQR 0.0–40) mg, median 20 (IQR 0.0–52) mg and median 0.0 (IQR 0.0–40) mg, while that for weeks 25–48 was median 0 (IQR 0–0) mg for all three arms, respectively.

The percentages of patients who reported at least one adverse event in the groups receiving active conventional therapy, certolizumab pegol, abatacept and tocilizumab were 88.3%, 89.6%, 85.8% and 96.7%, respectively (table 2), while at least one serious adverse event was reported in 10.7%, 12.4%, 8.3% and 9.2%, respectively. The number of early terminations was lowest for patients treated with abatacept (n=20), compared



**Figure 2** (A) Clinical Disease Activity Index remission rates over time (average marginal adjusted probabilities). (B) Cumulative probability plot of the radiographic progression from baseline to week 48, as assessed by the Total van der Heijde-modified Sharp Score.

with 38, 35 and 35 in the active conventional therapy, certolizumab pegol and tocilizumab arms, respectively (online supplemental figure S1). The numbers of patients who terminated due to lack of efficacy or adverse events were, respectively, 22 vs 2 for active conventional therapy, 7 vs 16 for certolizumab pegol, 7 vs 5 for abatacept and 1 vs 20 for tocilizumab; that is, patients on active active conventional therapy terminated almost exclusively due to lack of efficacy, while patients receiving tocilizumab almost exclusively terminated due to adverse events.

Of the prespecified adverse events of interest, infections were most frequent, being reported in 47.2%, 46.5%, 48.5% and 58.2% of patients treated with active conventional therapy, certolizumab pegol, abatacept and tocilizumab, respectively. Harms associated with glucocorticoid use (cataract, diabetes mellitus, osteoporosis and weight gain) were rare (each 0%–1.5% in all arms), and cardiovascular disease was reported in 2.0%, 4.0%, 5.9%, 3.8% of patients, respectively (see online supplemental tables S24–S29 for details).

## DISCUSSION

The NORD-STAR study is the first randomised trial to demonstrate that a biological therapy (or as the case is here, two different biological therapies) given as first-line therapy is clinically superior to conventional therapy even if the latter is optimised by the inclusion of bridging glucocorticoids.

This randomised head-to-head four-arm clinical trial of patients with treatment-naïve early RA showed clinical CDAI

remission at week 48 in approximately 40% of patients treated with active conventional therapy (MTX-based with glucocorticoid bridging therapy), whereas CDAI remission rates for the biological therapies were 50%–60%. For the selective costimulation modulator abatacept and the tumour necrosis factor (TNF) inhibitor certolizumab pegol, the remission rates were statistically significantly superior to active conventional therapy, with adjusted differences of +20.1% and +13.1%, respectively. In contrast, no difference in structural progression, as assessed by serial radiographs, was seen between treatments, and progression was very low in all groups. Key secondary clinical outcomes were numerically consistently better in biological groups compared with active conventional therapy.

The primary clinical outcome in the trial was remission according to CDAI, a more stringent remission criterion than the more commonly used DAS28-based. We chose the CDAI because its algorithm does not include acute-phase reactants, which are differentially impacted by different biological treatments and could therefore bias study outcomes.

Important differences between week 48 and week 24 results were observed. Particularly, the considerable advantage of biological therapies was much more pronounced at week 48 than at week 24.<sup>13</sup> The CDAI remission rate in the active conventional therapy group was slightly lower at week 48 than at week 24 (39.2% vs 42.7%), probably reflecting the decreasing effect of the initial bridging glucocorticoid therapy. Nevertheless, the main reason for the increasing difference between the biological arms and the active conventional therapy was that remission rates of biological arms increased markedly (abatacept: 52.0%–59.3%; certolizumab pegol 46.5%–52.3%; tocilizumab 42.1%–51.9%).

In early RA, pain and disability are mainly related to joint inflammation, but inhibition of structural progression is important for the long-term outcome, as even minor annual differences in structural progression will over decades accumulate and cause clinically significant pain and disability.<sup>15–30</sup> In the current study, the radiographic progression was low in all arms, and there were no differences between active conventional therapy and biological therapies. This highlights the advantage of glucocorticoid bridging, which immediately decreases inflammation, with the aim of both improving symptoms and decreasing structural progression. In contrast, other clinical trials using MTX without glucocorticoid bridging as comparison have reported an advantage on radiographic progression of biologics in early RA.<sup>31–33</sup> The administered glucocorticoid dose was in all treatment arms markedly lower during weeks 25–48 than during weeks 1–24, which reflects that the need for glucocorticoid declined with the gradual onset effect of the DMARDs. Another investigator-initiated treat-to-target study found DAS remission in 61% of RA patients after 4 months of MTX and oral glucocorticoid; in non-remission patients subsequently randomised to additional conventional DMARDs versus TNF-inhibitor, higher 1-year remission rates were found in patients treated with a TNF inhibitor.<sup>34</sup> An open-label treat-to-target trial applying MTX plus various doses of bridging glucocorticoids found rates of DAS-28 remission (less stringent than CDAI remission) at 2 years of approximately 60%,<sup>35</sup> that is, overall in accordance with our data.

Biological therapies are more costly than conventional therapy. Nevertheless, using a biological therapy as first-line therapy—after demonstration of clinical superiority—may be justified by the high direct and indirect costs of poorly controlled RA.<sup>36</sup> The introduction of the less expensive, but equally effective and safe, biosimilar drugs adds further

credence to that argument.<sup>37–39</sup> The cost-effectiveness should be confirmed in a dedicated analysis. Furthermore, several studies have suggested that after remission has been achieved, biologicals can often be tapered or discontinued safely.<sup>40–42</sup> This topic is the subject of the ongoing second part of the NORD-STAR trial.

Strengths of the study include the investigator-initiated set-up across six countries, allowing recruitment of >800 patients with early DMARD-naïve RA, with baseline characteristics typical for treatment-naïve poor-prognosis patients. The open-label design of this pragmatic trial is a limitation since it could influence certain subjective outcomes. We used blinded joint assessors to avoid bias on physician-determined outcomes. The active conventional therapy arm (arm 1) comprised two different treatment strategies based on national recommendations for conventional RA therapy in the individual countries. Analyses were adjusted for country effects, whereas the study was not powered for subgroup analyses.

No new safety signals were detected. Among prespecified events of interest, infections were common, particularly in the tocilizumab arm. An increased risk of adverse events attributable to glucocorticoid use was not found.

In conclusion, this large investigator-initiated randomised controlled trial showed a marked clinical superiority for two of the three biologicals in this study compared with active conventional therapy including MTX and glucocorticoids. We believe that the fact that two therapies (abatacept and certolizumab pegol) provide clinically and statistically significantly higher remission rates as compared with optimised conventional antirheumatic therapy with bridging glucocorticoids should be considered when the management of patients with newly diagnosed RA is decided, both in clinical practice and in treatment recommendations.

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**Contributors** MØ, RFvV, MLH, DCN, BG, EAH, KH-P, TU and GG designed the study and wrote the protocol. RFvV, MLH, MSH, DCN, SK, DG, NSK and EAH developed the CRFs. MØ, RFvV, AR, MLH, MSH, DCN, MTN, BG, KL, KH-P, TU, TS, GG, JLi, IG, DG, MCK, A-BA, FF, PP, TL, CG, JB, OH, DV TR, EG, MKL, EB, HL, AS, MR, AK, PL, LU, SAJ, DJS, TBL, GB, EAH and JLa contributed to the data collection and data cleaning. SK and NSK performed the data management. LMØ and PB read the radiographs. ICO wrote the statistical analysis plan, conducted the statistical analyses and made the figures. MØ wrote the manuscript with input from all authors. All authors had access to the raw dataset and vouch for the veracity of the results, and read and approved the final version of the manuscript including the decision to submit the

paper. MØ, RFvV, MLH, EAH and JLa are guarantors of the overall content, accept full responsibility for the work and the conduct of the study, had access to the data, and controlled the decision to publish. The corresponding author attests that all listed authors meet authorship criteria and that no other meeting the criteria has been omitted.

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**Data availability statement** Data are available upon reasonable request. Nordic Rheumatic Diseases Strategy Trials And Registries (NORD-STAR) data will not be shared publicly. Access to the NORD-STAR data is organised according to a strict data access procedure. For all types of access, a research proposal must be submitted for evaluation by the NORD-STAR Steering Committee. The evaluation is performed to align the goals of the researchers with the goals of NORD-STAR (which are in turn aligned with the informed consent form signed by NORD-STAR participants). Further information on NORD-STAR data can be obtained by contacting the NORD-STAR Steering Committee (mail to nordstar@ki.se).

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