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

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ABSTRACT

Background

The optimal first-line treatment in early rheumatoid arthritis 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, randomized, blinded-assessor study. Patients with treatment-naïve early rheumatoid arthritis with moderate-severe disease activity were randomized 1:1:1:1 to methotrexate combined with: 1) active conventional therapy: oral prednisolone (tapered quickly; discontinued at week 36); *or*: sulphasalazine, hydroxychloroquine and intra-articular corticosteroid injections in swollen joints; 2) certolizumab pegol; 3) abatacept or 4) tocilizumab. Co-primary endpoints were week 48 clinical disease activity index remission (CDAI≤2.8) and change in radiographic van der Heijde-modified Sharp Score, estimated using logistic regression and analysis of covariance, adjusted for sex, anti-citrullinated protein antibody status and country. Bonferroni's and Dunnet's procedures adjusted for multiple testing (significance level: 0.025).

Results

Eight-hundred-and-twelve patients were randomized. Adjusted CDAI remission rates at week 48 were: 59.3% (abatacept), 52.3% (certolizumab), 51.9% (tocilizumab) and 39.2% (active conventional therapy). Compared to 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.

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

Conclusions

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

Trial registration number: NCT01491815.

KEY MESSAGES

What is already known on this topic

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

What this study adds

- For the first time, 3 biologics with different modes of action, all in combination with methotrexate, were compared head-to-head against active conventional antirheumatic therapy with bridging corticosteroids in a randomized clinical trial in patients with early RA
- Compared to active conventional therapy, clinical remission rates were superior for abatacept and certolizumab pegol, while 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 rheumatoid arthritis

INTRODUCTION

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

Therefore, an investigator-initiated six-country collaboration was established to perform a randomized controlled trial, the Nordic Rheumatic Diseases Strategy Trials And Registries (NORD-STAR) study, to compare the benefits and harms of optimized conventional therapy ("active conventional therapy"), i.e. methotrexate combined with either oral corticosteroids or intra-articular corticosteroids and other csDMARDs) and three different biological therapies in combination with methotrexate (tumor-necrosis factor inhibitor (certolizumab pegol); T-cell costimulation modulator (abatacept); 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.[13] A comparison of the ability to halt structural damage progression, which is key to the longterm joint status and disability experienced by the patient,[14 15] 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 corticosteroid bridging therapy. Thus, inter-drug 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 methotrexate in patients with treatment-naïve rheumatoid arthritis.

METHODS

Study design

The design of this investigator-initiated, multicenter, randomized, open-label, blinded-assessor trial (https://clinicaltrials.gov/ct2/show/NCT01491815) has been published previously.[16] Patients were randomized to one of four different treatment arms aiming at achieving remission. This report decribes the analyses regarding the initial 48 weeks of the trial, including two co-primary (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 CONSORT statements.[17 18]. Patient representatitives were not involved in the design and conduct of this research.

Patients

Patients with early rheumatoid arthritis according to the American College of Rheumatology (ACR) and European Alliance of Associations for Rheumatology (EULAR) 2010 classification criteria were included (Table 1).[19] Key inclusion criteria were age ≥18 years; symptom duration <24 months; moderate to severe disease activity with DAS28>3.2 (disease activity score calculated from 28 swollen and tender joint counts, patient global score and C-reactive protein (CRP)); ≥2 (of 66) swollen and ≥2 (of 68) tender joints; and rheumatoid factor or anti-citrullinated protein antibody positivity (ACPA) or CRP ≥10mg/L. The key exclusion criterion was previous treatment with DMARD (see Supplementary Appendix for details).

Table 1: Demographics and patient characteristics at baseline (Intention to treat population).

Parameter	Active conventional therapy (n=200)	Certolizumab pegol and methotrexate (n=203)	Abatacept and methotrexate (n=204)	Tocilizumab and methotrexate (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)
Anti-citrullinated 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 (CDAI)	28.7 (12.1)	27.9 (12.4)	28.6 (11.3)	26.6 (11.7)
Disease activity score, 28 joints, CRP-based (DAS28)	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)
Health assessment questionnaire (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 - 8.5]	3 [1 - 8]	3 [1 - 6]	2 [0.5 - 5]
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 (standard deviation), if not otherwise indicated. § Seventeen Finnish patients randomized to arm 4 (TCZ+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.

IQR: Interquartile range, JSN: Joint space narrowing, n: Number of patients, Radiographic status: as assessed by van der Heijde-modified Sharp Score.

Randomization and procedures

Randomization was done 1:1:1:1, stratified by country, gender and ACPA status (See Supplementary Material for details).

All patients started methotrexate 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 (35mg/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 SC; Arm 4 (tocilizumab): 8 mg/kg/4weeks IV or 162 mg/week SC. In arms 2-4, intra-articular corticosteroid injections were allowed on demand up to week 12; thereafter up to 40 mg were allowed every 12 weeks. In all arms, intraarticular corticosteroids were prohibited in weeks 20-24 and 44-48 to minimize its influence on week 24/48 outcomes. Subjects were, as per investigator judgement, allowed to deescalate 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. NSAIDs were allowed throughout the study. Clinical examination included joint assessments for swelling and tenderness by independent blinded assessors. Patient reported outcomes included visual analogue scales (VAS) for pain and global assessment and physical function (Health Assessment Questionnaire (HAQ)). These and blood samples (including CRP) were acquired at weeks 0, 4, 8, 12, 16, 24, 32, 40 and 48)(Table 1).[16] 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 (0-10).[20]

Conventional radiographs of hands and feet were obtained at screening, week 24 and 48, and analyzed for bone erosion and joint space narrowing using the van der Heijde-modified Sharp Score (vdHSS), with known chronology, by two experienced, independent readers, blinded to all clinical data.[21] A total vdHSS (range 0-448) was calculated by adding erosion (0-280) and joint space narrowing (0-168) scores. The average of readers' scores was used. In case of reader discrepancies in change in total vdHSS (ΔTotal-vdHSSw0-w48) ≥2, a final score was reached by reader consensus.

Outcomes

The two co-primary outcomes were clinical remission at week 48 (Primary clinical outcome; defined as remission (CDAI≤2.8); dichotomous outcome)[20] and the change in radiographic score from baseline to week 48 (ΔTotal-vdHSSw0-w48; Primary radiographic outcome, continuous outcome)[21](Supplementary file 3, Statistical analysis plan (SAP)). In the protocol (Supplementary files 1-2), the co-primary outcomes were CDAI remission at week 24 and the above-mentioned change in radiographic score from baseline to week 48 (ΔTotal-vdHSSw0-w48). The 24-week clinical results, but no radiographic results, have been published previously[13]. For the 48 week analysis, the CDAI remission rate at week 48 was added as a co-primary outcome, prior to any analyses (Supplementary file 3, Statistical analysis plan (SAP).

Key secondary clinical outcomes were ACR/EULAR Boolean remission, DAS28 remission, simplified disease activity index (SDAI) remission and EULAR good response at week 48[20 22 23]. Key secondary radiographic outcomes were: No radiographic progression (ΔvdHSS from baseline to 48

weeks <1), changes from baseline to week 48 in vdHSS erosion scores and vdHSS joint space narrowing (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 Supplementary file 3 (SAP) and Supplementary appendix, Tables S1-S7)

Safety outcomes were the numbers and percentages of patients with serious and non-serious adverse events for each treatment arm. Pre-defined adverse events of special interest are defined in Table 3. All safety events were MedDRA coded (v.22.0).

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 [3 24-28] (see [13] for details).

This part of the trial was designed to establish the superiority of at least one of the biologic treatments compared to active conventional therapy at 48 weeks on (1) achieving CDAI remission; (2) preventing progression in the radiographic Sharp-van der Heijde 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 Dunnet's method when having a common comparator. [29]

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 Supplementary file 3 (SAP)). Primary and secondary dichotomous outcomes

were analysed using a logistic regression model, adjusted for stratification factors in the randomization (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 (ANCOVA), adjusted for baseline score and the stratification factors in the randomization. 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 Supplementary file 3 (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 December 3rd 2012 to December 11th 2018, whereof 812 underwent randomization and 625 completed week 48 visit (last patient on November 12th, 2019; Supplementary Figure S1: Patient disposition). Patient characteristics were well balanced (Table 1). The patients (68.8% women, 81.9% ACPA postive, 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 2, Figure 1A). The null hypotheses were formally rejected for active

conventional therapy vs abatacept (adjusted difference +20.1%; adjusted p<0.001) and active conventional therapy vs certolizumab pegol (+13.1%; p=0.021), but not for active conventional therapy vs tocilizumab (+12.7%; p=0.030), given that the cutoff 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 mean change in the total van der Heijde-modified Sharp score from baseline to week 48 (ΔTotal-vdHSSw0-w48) was 0.45 for active conventional therapy, 0.62 for abatacept, 0.47 for certolizumab pegol and 0.50 for tocilizumab, i.e. consistently low (Figure 1B). No statistically significant differences in ΔTotal-vdHSSw0-w48 were found between groups (Table 2). Figure 2B presents a cumulative probability plot of the radiographic progression.

Table 2: Primary and key secondary outcomes at week 48 (Intention to treat population)

	Active conventional therapy (n=200)	**Certolizumab pegol and methotrexate (n=203)**	**Abatacept and methotrexate (n=204)**	**Tocilizumab and methotrexate (n=188) §**
Estimated adjusted outcome (ITT population)[1]				
Co-primary outcomes				
CDAI remission, w48	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 w0-w48	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)
Key secondary outcomes				
ACR/EULAR Boolean remission, w48	31.6% (25.3 to 38)	46.3% (39.5 to 53.1)	51% (44.2 to 57.8)	44.6% (37.6 to 51.6)
DAS28 remission,w48	53.7% (46.9 to 60.6)	66.6% (60.1 to 73)	71.1% (65 to 77.3)	68.2% (61.6 to 74.7)
SDAI remission, w48	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, w48	66.4% (59.9 to 72.9)	74.6% (68.7 to 80.6)	77.7% (72 to 83.4)	69.3% (62.8 to 75.9)
Radiographic progression, Total ≤0.5, w0-w48	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 w0-w48	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 w0-w48	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)[2]				
Co-primary Outcomes				
CDAI remission, w48	Reference	13.1% (3.5 to 22.6)*	20.1% (10.6 to 29.5)**	12.7% (3 to 22.5)
ΔvdHSS Total w0-w48	Reference	0.02 (-0.17 to 0.22)	0.17 (-0.02 to 0.37)	0.05 (-0.15 to 0.25)
Key secondary outcomes				
ACR/EULAR Boolean remission, w48	Reference	14.7% (5.4 to 23.9)	19.4% (10.1 to 28.7)	13% (3.5 to 22.4)
DAS28 remission,w48	Reference	12.9% (3.5 to 22.2)	17.4% (8.2 to 26.6)	14.4% (5 to 23.9)
SDAI remission, w48	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, w48	Reference	8.2% (-0.6 to 17.1)	11.3% (2.7 to 20)	2.9% (-6.3 to 12.2)
Radiographic progression, Total progression ≤0.5, w0-w48	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 w0-w48	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 w0-w48	Reference	0 (-0.13 to 0.13)	0.08 (-0.05 to 0.21)	0.01 (-0.12 to 0.14)

[1]For dichotomous variables, values are estimated adjusted marginal proportions or estimated 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).

[2]For 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 intra- or extrapolation.

Results are based on the intention to treat population; 17 Finnish patients allocated to tocilizumab and methotrexate group excluded([§]), since they could not receive tocilizumab because the drug was not available in the Finnish part of the study.

**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, bDMARD: Biological disease modifying anti-rheumatic drug, CDAI: Clinical disease activity index; CZP: Certolizumab pegol, DAS28: Disease activity score (28 joints, 4 variables, C-reactive protein), EULAR, European Alliance of Associations for Rheumatology, IQR: Interquartile range, JSN: Joint space narrowing, n: Number of patients, SDAI: Simplified disease activity index, ITT: intention to treat, Radiographic progression: as assessed by van der Heijde-modified Sharp Score, TCZ: Tocilizumab.

Key secondary clinical outcomes were consistently numerically better in bDMARD groups compared to active conventional therapy for all remission criteria, with the abatacept group being numerically the best (Table 2). All key secondary radiographic outcomes were comparable across treatment groups (Table 2).

Results of other secondary clinical and radiographic outcomes can be found in Supplementary Tables S1-S7. The course over time of selected outcomes is depicted in Supplementary Figures S2-S14.

The smallest detectable difference (SDC) in ΔTotal-vdHSSw0-w48 was 1.43. The proportion of patients showing progression above SDC (ΔTotal-vdHSSw0-w48>SDC), reflecting progression above measurement error, in active conventional therapy, 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 (ΔTotal-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 (Supplementary Tables S8-S23). Corticosteroid use was mandatory in arm 1. In arm 1A, prednisolone was reduced from 20 to 5 mg in nine 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 intraarticular triamcinolone hexacetonide equivalents from week 0 to week 48 were 18 (0-49) mg (median(IQR), 20 (0-60) mg, and 0 (0-40) mg, respectively, while it was 70 (50-103) mg in arm 1B and 0 (0-18 mg) in arm 1A. The median cumulative dose of 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 triamcinolone hexacetonide was median 66 (IQR 40-94) mg from week 1-24, while only 0 (0-10 mg) from week 25 to 48. In arm 1A the cumulative dose of triamcinolone hexacetonide was median 0 (0-6) mg from week 1 to 24, while 0 (0-0 mg) from week 25-48.

In the certolizumab-pegol, abatacept, and tocilizumab arms the cumulative doses of triamcinolone hexacetonide from week 0 to week 24 were 12 (0.0-40) mg, 20 (0.0-52) mg, and 0.0 (0.0-40) mg, while 0 (0-0) mg for all 3 arms from week 25 - 48, 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 3), 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 to 38, 35 and 35 in the active conventional therapy, certolizumab pegol and tocilizumab arms, respectively (Supplementary 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, i.e 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 corticosteroid 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 Supplementary tables S24-S29 for details).

Table 3. Adverse events in the safety population§. Values are: [number of events], no of patients (percentage of patients in that arm who experienced at least one event)

Parameter[#]	Active conventional therapy (N=197)	Certolizumab pegol and methotrexate (N=202)	Abatacept and methotrexate (N=204)	Tocilizumab and methotrexate (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%)

*§Adverse events are summarized by the safety population, and by actual treatment (not as randomized). Thus, the 17 Finnish patients randomized to arm 4 (tocilizumab) but not receiving it due to unavailability are not included. #[events] no of patients (percentage of patients in that arm). Patients could have more than one category of events. *Patient 1: Sudden death in 78 year old woman. A lump in the breast was discovered at the screening visit, later breast cancer was diagnosed. She terminated early in the trial on study day 42, had mastectomy on study day 47 and died suddenly thereafter on study day 102. The events were assessed as not related to study drug by the investigator. Patient 2: This patient had dyspnea as an adverse event that started just before the Week 24 visit. She was hospitalized on Day 197 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 shortly thereafter (Day 215). 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, e.g. based on baseline DXA scan.*

DISCUSSION

The NORD-STAR study is the first randomized 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 optimized by the inclusion of bridging corticosteroids.

This randomized head-to-head 4-arm clinical trial of patients with treatment-naïve early rheumatoid arthritis showed clinical CDAI remission at week 48 in approximately 40% of patients treated with active conventional therapy (methotrexate-based with corticosteroid bridging therapy), whereas CDAI remission rates for the biological therapies were 50-60%. For the selective costimulation modulator abatacept and the TNF-inhibitor certolizumab pegol the remission rates were statistically significantly superior to active conventional therapy, with adjusted differences +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 to 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 biologic 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.[13] 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 corticosteroid 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% to 59.3%; certolizumab pegol 46.5% to 52.3%; tocilizumab 42.1% to 51.9%).

In early rheumatoid arthritis, pain and disability are mainly related to joint inflammation, but inhibition of structural progression is important for the longterm outcome, as even minor annual differences in structural progression will over decades accumulate and cause clinically significant pain and disability.[15 30] 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 corticosteroid bridging, which immediately decreases inflammation, with the aim of both improving symptoms and decreasing structural progression. In contrast, other clinical trials using methotrexate without corticosteroid bridging as comparison have reported an advantage on radiographic progression of biologics in early RA.[31-33] The administereed corticosteroid dose was in all treatment arms markedly lower during weeks 25-48 than during weeks 1-24, which reflects that the need for corticosteroid 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 corticosteroid; 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.[34] An open-label treat-to-target trial applying methotrexate plus various doses of bridging corticosteroids found rates of DAS-28 remission (less stringent than CDAI remission) at 2 years of approximately 60%[35], i.e. 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 rheumatoid arthritis.[36] The introduction of the less expensive, but equally effective and safe, biosimilar drugs adds further credence to that argument.[37-39] 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. [40-42] 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 rheumatoid arthritis, 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.

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 corticosteroid use was not found.

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

CONTRIBUTORS

MØ, RvV, MLH, DN, BG, EAH, KHP, TU and GG designed the study and wrote the protocol. RvV, MLH, MSH, DN, SK, DG, Niels Steen Krogh and EAH developed the CRFs. MØ, RvV, AR, MLH, MSH, DN, MN, BG, KL, KHP, TU, TSI, GG, JL, IG, DG, MK, ABA, FF, PP, TL, CG, JB, OH, DV TR, EG, MKL, EB, HML, AS, MR, AK, PL, LU, SAJ, DJS, TBL, GB, EAH, JL contributed to the data collection and data cleaning. SK and Niels Steen Krogh did data management. LØ 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. All authors read and approved the final version of the manuscript including the decision to submit the paper. MØ, RvV, MLH, EAH and JL 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 others meeting the criteria have been omitted.

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DECLARATION OF INTERESTS

All authors have completed the ICMJE uniform disclosure form at http://www.icmje.org/coi_disclosure.pdf.

The disclosures of the individual authors are summarized below:

Mikkel Østergaard received study drug from BMS and UCB, has received research grants from Abbvie, BMS, Merck, Novartis and UCB, and speaker fees from Abbvie, BMS, Celgene, Eli-Lilly, Galapagos, Gilead, Janssen, MEDAC, Merck, Novartis, Pfizer, Sandoz, and UCB and consultancy fees from Abbvie, BMS, Celgene, Eli-Lilly, Galapagos, Gilead, Janssen, MEDAC, Merck, Novartis, Pfizer, Sandoz, and UCB.

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COMPETING INTERESTS

All authors will complete the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf. This will be provided after the initial review or earlier if requested.

ETHICAL APPROVAL

The study was approved by national medical agencies, institutional review boards and independent ethics committees in participating countries and was conducted in accordance with national regulations and the International Conference on Harmonization Good Clinical Practice requirements, based on the Declaration of Helsinki. Names of the ethics committees and ID# were: Regionala etikprövningsnämnden i Stockholm, ID: 2011/2069-31/4 (Sweden); Den Videnskabsetiske Komite for Region Hovedstaden, ID: H-2-2013-153 (Denmark); Regional committees for medical and health research ethics, ID: 2014/2191/REC South East (Norway);

Ethics Committee of Internal Medicine at the Helsinki University Hospital (HUS), ID: 240/13/03/01/2012 (Finland); Medisch Ethische Toetsingscommissie voor het Slotervaartziekenhuis en Reade, ID: NL60775.048.17 (The Netherlands); The National Bioethics Committee (NBC) Iceland; ID: 13-085 (Iceland). All the patients provided written informed consent before any study-related procedures.

DATA SHARING

NORD-STAR data will not be shared publicly. Access to the NORD-STAR data is organized 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).

FIGURE LEGENDS

Figure 1: Plots of the co-primary outcomes: A. Clinical remission at week 48 (Adjusted Clinical Disease Activity Index (CDAI) remission rates at week 48). 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. 95% confidence intervals are shown.

Figure 2. A. CDAI remission rates over time (Average marginal adjusted probablities); B. Cumulative probability plot of the radiographic progression from baseline to week 48, as assessed by the van der Heijde-modified Total Sharp score.

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