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phase IV investigator initiated, randomised, observer blinded clinical trial

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Active conventional treatment and three different biological treatments in early rheumatoid arthritis: phase IV investigator initiated, randomised, observer blinded clinical trial

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ABSTRACT

OBJECTIVE

To evaluate and compare benefits and harms of three biological treatments with different modes of action versus active conventional treatment in patients with early rheumatoid arthritis.

DESIGN

Investigator initiated, randomised, open label, blinded assessor, multiarm, phase IV study.

SETTING

Twenty nine rheumatology departments in Sweden, Denmark, Norway, Finland, the Netherlands, and Iceland between 2012 and 2018.

PARTICIPANTS

Patients aged 18 years and older with treatment naïve rheumatoid arthritis, symptom duration less than 24 months, moderate to severe disease activity,

and rheumatoid factor or anti-citrullinated protein antibody positivity, or increased C reactive protein.

INTERVENTIONS

Randomised 1:1:1:1, stratified by country, sex, and anti-citrullinated protein antibody status. All participants started methotrexate combined with (a) active conventional treatment (either prednisolone tapered to 5 mg/day, or sulfasalazine combined with hydroxychloroquine and intra-articular corticosteroids), (b) certolizumab pegol, (c) abatacept, or (d) tocilizumab.

MAIN OUTCOME MEASURES

The primary outcome was adjusted clinical disease activity index remission (CDAI≤2.8) at 24 weeks with active conventional treatment as the reference. Key secondary outcomes and analyses included CDAI remission at 12 weeks and over time, other remission criteria, a non-inferiority analysis, and harms.

RESULTS

812 patients underwent randomisation. The mean age was 54.3 years (standard deviation 14.7) and 68.8% were women. Baseline disease activity score of 28 joints was 5.0 (standard deviation 1.1). Adjusted 24 week CDAI remission rates were 42.7% (95% confidence interval 36.1% to 49.3%) for active conventional treatment, 46.5% (39.9% to 53.1%) for certolizumab pegol, 52.0% (45.5% to 58.6%) for abatacept, and 42.1% (35.3% to 48.8%) for tocilizumab. Corresponding absolute differences were 3.9% (95% confidence interval −5.5% to 13.2%) for certolizumab pegol, 9.4% (0.1% to 18.7%) for abatacept, and −0.6% (−10.1% to 8.9%) for tocilizumab. Key secondary outcomes showed no major differences among the four treatments. Differences in CDAI remission rates for active conventional treatment versus certolizumab pegol and tocilizumab, but not abatacept, remained within the prespecified non-inferiority margin of 15% (per protocol population). The total number of serious adverse events was 13 (percentage of patients who experienced at least one event 5.6%) for active

WHAT IS ALREADY KNOWN ON THIS TOPIC

Rheumatoid arthritis is associated with joint destruction, pain, functional impairment, and increased comorbidity and mortality

The optimal first line treatment has been debated, especially whether it should include a biological disease modifying drug

With multiple biological treatments, whose benefits and harms have not been compared in treatment naïve patients, it is unclear whether one or more biological drugs might be more beneficial or safer in patients with early rheumatoid arthritis

WHAT THIS STUDY ADDS

This trial compared the benefits and safety of three biological drugs with different modes of action, all given in combination with methotrexate, versus active conventional treatment in treatment naïve patients with rheumatoid arthritis

At 24 weeks, higher clinical disease activity index (CDAI) remission rate was observed for abatacept versus active conventional treatment (9.4%), but not for certolizumab pegol (3.9%) or tocilizumab (−0.6%) versus active conventional treatment

Non-inferiority analysis indicated that active conventional treatment was non-inferior to certolizumab pegol and tocilizumab, but not to abatacept

conventional treatment, 20 (8.4%) for certolizumab pegol, 10 (4.9%) for abatacept, and 10 (4.9%) for tocilizumab. Eleven patients treated with abatacept stopped treatment early compared with 20-23 patients in the other arms.

CONCLUSIONS

All four treatments achieved high remission rates. Higher CDAI remission rate was observed for abatacept versus active conventional treatment, but not for certolizumab pegol or tocilizumab versus active conventional treatment. Other remission rates were similar across treatments. Non-inferiority analysis indicated that active conventional treatment was non-inferior to certolizumab pegol and tocilizumab, but not to abatacept. The results highlight the efficacy and safety of active conventional treatment based on methotrexate combined with corticosteroids, with nominally better results for abatacept, in treatment naïve early rheumatoid arthritis.

TRIAL REGISTRATION

EudraCT2011-004720-35, NCT01491815.

Introduction

Rheumatoid arthritis is a chronic inflammatory joint disease associated with joint destruction, pain, functional impairment, and increased comorbidity and mortality.^{1 2} Early and active treatment is associated with improved outcome.³ The optimal first line treatment for patients with early rheumatoid arthritis has been debated, especially whether it should include a biological disease modifying drug.⁴ Currently, treatment recommendations in Europe and the United States advocate early treatment with conventional slow acting synthetic disease modifying drugs, with methotrexate as the anchor drug.^{4 5} The addition of short term low to moderate dose corticosteroids to methotrexate (termed active conventional treatment) might optimise results.^{4 6-8} Biological disease modifying antirheumatic drugs with different modes of action have been marketed. The most frequently used treatments prescribed early in the disease course are tumour necrosis factor α inhibition, T cell costimulation blocker, and interleukin 6 inhibition. Previous trials have shown superior outcomes in treatment naïve patients who have received biological drugs in combination with methotrexate compared with methotrexate and placebo.⁹⁻¹³ Several biological drugs are available whose benefits and harms need to be compared with one another in treatment naïve patients. Studies are needed to determine whether one or more biologicals might be more beneficial or safer, or better tailored to different subgroups of patients with rheumatoid arthritis. Therefore, a consortium of Scandinavian and Dutch academic investigators planned and conducted a randomised trial examining the comparative benefits and safety of biological drugs with different modes of action versus active conventional treatment in treatment naïve patients with rheumatoid arthritis.

In the first part of the NOrdic Rheumatic Diseases Strategy Trials And Registries (NORD-STAR) study

our objective was to assess and compare the efficacy and safety after 24 weeks of active conventional treatment (either methotrexate combined with oral corticosteroids or methotrexate combined with intra-articular corticosteroids and other conventional synthetic disease modifying antirheumatic drugs) versus three biological treatments: a tumour necrosis factor inhibitor (certolizumab pegol), a T cell costimulation blocker (abatacept), and an interleukin 6 inhibitor (tocilizumab), all given in combination with methotrexate. Our hypothesis was that a higher clinical disease activity index (CDAI) remission rate would be observed for one or several of the biologicals compared with active conventional treatment.

Methods

Trial design and conduct

The design of this investigator initiated, multicentre, randomised, open label, blinded assessor trial (ClinicalTrials.gov: NCT01491815) has been published previously.¹⁴ The protocol is included in the online supplementary files. The trial has two parts: initial randomisation to one of four different treatment arms aiming to achieve remission (up to 80 weeks' follow-up); and rerandomisation to two different tapering strategies of patients who reach the remission target. We present the 24 week analyses of the primary clinical outcome and key secondary outcomes. A steering committee of academic investigators designed and oversaw the trial. They also analysed and interpreted the data and contributed to the manuscript. We report our findings in accordance with the CONSORT (Consolidated Standards of Reporting Trials) statements, including the extension for multiarm, parallel group randomised trials.¹⁵⁻¹⁷

Study population

The trial population consisted of patients with early rheumatoid arthritis according to the American College of Rheumatology and European League Against Rheumatism (ACR/EULAR) 2010 classification criteria.¹⁸ Key inclusion criteria were age 18 years or older, symptom duration less than 24 months, moderate to severe disease activity with disease activity score (DAS28) greater than 3.2 (DAS28 calculated from 28 swollen and tender joint counts, patient global score, and C reactive protein), at least two (of 66) swollen and at least two (of 68) tender joints, and rheumatoid factor or anti-citrullinated protein antibody positivity (ACPA), or C reactive protein at least 10 mg/L. Key exclusion criteria included previous treatment with disease modifying antirheumatic drugs. Table S1 provides details about the inclusion and exclusion criteria.

Randomisation and interventions

Patients were randomised 1:1:1:1, stratified by country, sex, and ACPA status. Randomisation was done through the trial centre at the Karolinska Institute (see supplementary appendix for details). All patients started methotrexate on day 1 (escalated within four weeks to 25 mg every week) with folic

acid supplementation (minimum 5 mg every week) combined with one of the following:

- Arm 1 (active conventional treatment)—either (a) oral prednisolone (tapered from 20 to 5 mg/day in nine weeks); or (b) enterotablets sulfasalazine (2 g/day) combined with hydroxychloroquine (35 mg/kg every week or 200 mg/day) and mandatory intra-articular triamcinolone hexacetonide injection (or equivalent) in all swollen joints at each visit (maximally four joints and 80 mg every visit and no later than week 20)
- Arm 2 (certolizumab pegol)—200 mg every other week subcutaneously (loading dose 400 mg at week 0, 2, and 4)
- Arm 3 (abatacept)—125 mg every week subcutaneously
- Arm 4 (tocilizumab)—8 mg/kg every four weeks intravenously or 162 mg every week subcutaneously.

Intra-articular corticosteroid injections were allowed on demand up to week 20 in arm 1 and up to week 12 in arms 2–4; for details see protocol and statistical analysis plan in supplementary files.¹⁴ Patients received folate, vitamin D, and calcium supplementation according to local or national guidelines.

Trial outcomes and blinding

The primary clinical efficacy outcome was adjusted CDAI remission (defined as $\text{CDAI} \leq 2.8$) at week 24.¹⁹ CDAI is 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). An independent blinded assessor with no other roles in the study conducted the joint counts. Key secondary efficacy outcomes included CDAI remission at week 12 and over time (at week 4, 8, 12, 16, and 24); and other remission criteria at week 12, week 24, and over time: ACR/EULAR Boolean criteria, DAS28 and simplified disease activity index remission, and EULAR good response (see statistical analysis plan in supplementary files).^{20–23}

Safety outcomes were the numbers and percentages of patients with serious and non-serious adverse events for each treatment arm. Predefined adverse events of interest included infections, cardiovascular disease, cataract, venous thromboembolism, demyelinating disease, diabetes mellitus, herpes zoster, malignancy, osteoporosis, tuberculosis, and weight gain. All safety events were MedDRA coded (version 22.0).

Statistical analysis

This was a phase IV trial done in a clinical setting, not a confirmatory phase III trial. Therefore, as prespecified in the statistical analysis plan, effect estimates and 95% confidence intervals are reported for the differences between treatment arms at specific time points. Formal hypothesis tests were not performed, and confidence limits were not adjusted for multiplicity (see the statistical framework and statistical analysis plan in supplementary files).

The a priori sample size calculation indicated that we needed to randomise 724–832 patients to detect an overall difference between the four treatment groups with a power of 85–90%, assuming CDAI remission rates of 12%, 22%, 22%, and 26% in the active conventional treatment, certolizumab pegol, abatacept, and tocilizumab arms, respectively^{9–11 24–28} (see protocol and statistical framework for details). We expected one or several of the three biological drugs to have higher remission rates than the active conventional treatment. The three comparisons were conducted in parallel, with inference made in each comparison.

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 statistical analysis plan in supplementary files). Strictly interpreted, these patients should have remained in the intention-to-treat population with non-responder imputation. Instead, the steering committee decided before data lock to exclude them from the intention-to-treat population to allow a fair analysis of the efficacy of tocilizumab. For transparency, the results of the analyses conducted on the strict intention-to-treat population are presented in the supplementary appendix.

The primary analysis of the primary and secondary dichotomous outcomes was done using a logistic regression model, adjusted for sex, ACPA status, country, age, body mass index, and DAS28 at baseline, with missing remission status imputed with worst case (non-remission). We present adjusted average marginal differences in remission rates with 95% confidence intervals, estimated by the delta method. Robustness analyses were performed using unadjusted logistic regression and longitudinally using adjusted and unadjusted generalised estimating equations, accounting for within patient correlation. Generalised estimating equations used non-imputed data with an exchangeable correlation structure. Robustness analyses were also performed and included the 17 Finnish patients mentioned above. Continuous secondary outcomes were analysed using generalised linear mixed gamma (C reactive protein and erythrocyte sedimentation rate), negative binomial (joint counts), or normal models (other), all with random intercept adjusted for baseline characteristics and value. Some of the other secondary outcomes are not reported here; we will report them in a separate publication (table S15 gives details).

We conducted non-inferiority analyses in the per protocol population, which consisted of patients who received study drugs as planned, by predefining a margin of 15% based on previous trials (see statistical analysis plan and statistical framework in supplementary files).^{29 30} For safety outcomes, descriptive statistics were applied on the safety population.

Patient and public involvement

Patients or the public were not involved in the design, or conduct, or reporting of the study, but the patient organisations of the involved countries will be involved in the dissemination plans of our research.

Results

Participants

From 3 December 2012 to 11 December 2018, 903 patients were assessed for eligibility at 29 sites (listed in supplementary files). The proportion of screened patients who did not undergo randomisation was 10% (91/903); 812 underwent randomisation (fig S1). The last 24 week visit was conducted on 28 May 2019. Patient characteristics were well balanced (table 1). The mean age was 54.3 years, 68.8% of the patients were women, average symptom duration was 204 days, and mean time since diagnosis was 14 days. Disease activity was moderate to severe, with an average DAS28 of 5.0 and CDAI of 28.0. Rheumatoid factor was positive in 74.7% of patients, while 81.9% were ACPA positive.

Efficacy outcomes

Table 2 summarises efficacy outcomes. The adjusted CDAI remission rate at 24 weeks was 42.7% (95% confidence interval 36.1% to 49.3%) for patients in the active conventional treatment group, 46.5% (39.9% to 53.1%) for the certolizumab pegol group, 52.0% (45.5% to 58.6%) for the abatacept group, and 42.1% (35.3% to 48.8%) for the tocilizumab group. With active conventional treatment as the reference, the adjusted difference in CDAI remission rate was 3.9% (95% confidence interval -5.5% to 13.2%) for certolizumab pegol, 9.4% (0.1% to 18.7%) for abatacept, and -0.6% (-10.1% to 8.9%) for tocilizumab. The adjusted CDAI remission rates at 12 weeks were largely similar across treatments; with active conventional treatment as the reference, the remission rates were 4.5%, 2.6%, and 4.6% higher for certolizumab pegol, abatacept, and tocilizumab, respectively. The mean adjusted difference in CDAI remission over time was 6.3% (-0.4% to 12.9%) for certolizumab pegol, 1.5% (-5.0% to 7.9%) for abatacept, and 2.0% (-4.7% to 8.7%) for tocilizumab. Figure 1 shows that for adjusted CDAI remission rates over time no clear separation was found between the four treatment arms. For key secondary outcomes, results were generally similar across the four treatment groups (table 2, figs S3-S6). Table S2 and figs S7-S13 present results for other secondary outcomes.

Robustness analyses

We conducted prespecified robustness analyses of the primary and key secondary efficacy outcomes. The results were consistent with those of the primary analyses (fig S14 and tables S3-S5).

Non-inferiority analyses

For CDAI remission at 24 weeks, differences in remission rates for the active conventional treatment versus certolizumab pegol and tocilizumab, but not abatacept, remained within the predefined non-inferiority margin of 15% (fig 2). Tables S6-S7 show the results of the non-inferiority analyses.

Corticosteroids

The use of corticosteroids was mandatory in arm 1, either orally (bridging treatment with tapering, arm 1A, n=137) or as mandatory injections of swollen joints (arm 1B, n=63). In arm 1A, prednisolone was reduced from 20 to 5 mg in nine weeks, then kept stable (5 mg) through week 32, then reduced and stopped at week 36. In arm 1B, from week 0 to week 4 the cumulative dose of triamcinolone hexacetonide corresponded to a median of 50 mg (interquartile range 34-80 mg), increasing to a total of 66 (40-94) mg by week 24. In the certolizumab pegol, abatacept, and tocilizumab arms the cumulative doses from week 0 to week 24 were 20 (0.0-80) mg, 20 (0.0-80) mg, and 0.0 (0.0-40) mg triamcinolone hexacetonide, respectively. The median cumulative dose of triamcinolone hexacetonide corresponded to a daily dose of less than 1 mg prednisolone in arm 1B and less than 0.5 mg in the certolizumab pegol and abatacept arms under the assumption that 40 mg of triamcinolone is equivalent to 50 mg of prednisolone.

Safety outcomes and adherence to treatment

No suspected unexpected harms were reported. The percentages of patients who reported at least one adverse event in the groups receiving active conventional treatment, certolizumab pegol, abatacept, and tocilizumab were 86.3%, 82.7%, 79.9%, and 95.1%, respectively (table 3); at least one serious adverse event was reported in 5.6%, 8.4%, 4.9%, and 4.9% of patients, respectively. The number of patients who stopped treatment early was lowest for patients receiving abatacept (11 patients), compared with 20, 23, and 22 patients in the active conventional treatment, certolizumab pegol, and tocilizumab arms, respectively. Figure S1 gives the reasons for stopping treatment early.

Of the prespecified adverse events of interest, infections were reported in 34.5%, 36.6%, 34.3%, and 45.7% of patients treated with active conventional treatment, certolizumab pegol, abatacept, and tocilizumab, respectively. Harms associated with corticosteroid use (cataract, diabetes mellitus, osteoporosis, and weight gain) were rare (0-1.5% in all arms), and cardiovascular disease was reported in 1.5%, 3.5%, 4.4%, and 3.3% of patients, respectively.

Gastrointestinal symptoms were reported in 42.1%, 29.7%, 37.3%, and 29.9% of patients treated with active conventional treatment, certolizumab pegol, abatacept, and tocilizumab, respectively (table S14). Increased liver enzymes were reported in 10.7%, 14.4%, 14.2%, and 30.4%, and increased neutropenia or leukopenia in 1%, 1%, 1.5%, and 12.5% of patients, respectively. For more details on harms, see tables S9-S14.

Discussion

Statement of principal findings

We found that CDAI remission was achieved in more than 40% of patients with treatment naïve

Table 1 | Personal and clinical characteristics of patients at baseline (intention-to-treat population). Values are means (standard deviations) unless stated otherwise

Characteristic	Active conventional treatment (n=200)	Certolizumab pegol and methotrexate (n=203)	Abatacept and methotrexate (n=204)	Tocilizumab and methotrexate (n=188)
Age (years)	54.6 (14.5)	55.3 (15.3)	54.7 (14.4)	52.4 (14.5)
Women (n (%))	139 (69.5)	139 (68.5)	140 (68.6)	129 (68.6)
Symptom duration (days)	195 (167)	203 (166)	212 (168)	208 (155)
Time since diagnosis (days)	13 (21)	12 (17)	16 (34)	16 (33)
Body mass index*	26.6 (5.4)	25.7 (4.9)	26 (4.9)	26.8 (5.1)
Non-smoker (n (%))	80 (40)	76 (37.4)	77 (37.7)	85 (45.2)
Former smoker (n (%))	85 (42.5)	79 (38.9)	78 (38.2)	60 (31.9)
Current smoker (n (%))	35 (17.5)	47 (23.2)	49 (24)	43 (22.9)
Anti-citrullinated peptide antibody positive (n (%))	163 (81.5)	166 (81.8)	169 (82.8)	153 (81.4)
Rheumatoid factor positive (n (%))	151 (75.5)	149 (73.4)	159 (77.9)	135 (71.8)
Clinical disease activity index (CDAI)	28.6 (12.1)	27.9 (12.4)	28.6 (11.3)	26.6 (11.7)
Disease activity score of 28 joints (CRP based)	5.1 (1.1)	5.0 (1.1)	5.1 (1)	4.9 (1)
Tender joint count (68 joints)	17 (11.4)	15.3 (10.4)	16.1 (10.7)	14.8 (10.2)
Swollen joint count (66 joints)	11.4 (7.3)	11.2 (7.6)	11.1 (7.3)	9.8 (6.4)
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 (mm)	48.8 (19.2)	49.3 (19.2)	51.7 (18.7)	49.7 (18.1)
Patient's assessment of pain (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)

CRP=C reactive protein.

*Two patients had missing value for body mass index at baseline. The missing values were imputed with the median.

early rheumatoid arthritis who were treated with biological drugs with different modes of action (certolizumab pegol, abatacept, or tocilizumab), which were all given in combination with methotrexate. Patients who received active conventional treatment (methotrexate combined with bridging treatment with corticosteroids, and in some patients also sulfasalazine and hydroxychloroquine) had comparable remission rates. With the active conventional treatment as the reference, abatacept performed 9% better in achieving CDAI remission (primary efficacy outcome). For all key secondary outcomes, including longitudinal analysis and a range of other remission and response criteria, the overall differences between treatments were modest with overlapping confidence intervals. A prespecified non-inferiority analysis of the primary outcome

showed that active conventional treatment was non-inferior to certolizumab pegol and tocilizumab, but not to abatacept. Among the prespecified harms of interest, serious adverse event rates were highest in the certolizumab pegol group, whereas infection rates and events of increased hepatic enzymes and neutropenia or leukopenia were higher in the tocilizumab arm. We found no increased risk of adverse events attributable to corticosteroid use in the active conventional treatment arm, whereas gastrointestinal symptoms were most common in this arm.

Strengths and weaknesses of the study

This randomised clinical trial examined the comparative benefits and safety of biological drugs with different modes of action versus active conventional

Table 2 | Primary and key secondary outcomes. Values are percentage differences in rates (95% confidence intervals) with active conventional treatment as reference

Parameter	Week No	Certolizumab pegol and methotrexate v active conventional treatment	Abatacept and methotrexate v active conventional treatment	Tocilizumab and methotrexate v active conventional treatment
Primary outcome				
CDAI remission	24	3.9 (−5.5 to 13.2)	9.4 (0.1 to 18.7)	−0.6 (−10.1 to 8.9)
Key secondary outcomes				
CDAI remission	12	4.5 (−4.4 to 13.3)	2.6 (−6.1 to 11.4)	4.6 (−4.4 to 13.7)
ACR/EULAR Boolean remission	24	3.6 (−5.7 to 12.9)	4.6 (−4.6 to 13.9)	−3.8 (−13.2 to 5.6)
ACR/EULAR Boolean remission	12	7.1 (−1.3 to 15.6)	7.2 (−1.2 to 15.7)	9.2 (0.5 to 18)
DAS28 remission	24	2.6 (−6.2 to 11.4)	4.5 (−4.2 to 13.2)	−0.7 (−9.8 to 8.4)
DAS28 remission	12	5.8 (−3.3 to 14.9)	2.2 (−6.9 to 11.3)	14 (4.8 to 23.1)
SDAI remission	24	6.4 (−3 to 15.7)	8.9 (−0.3 to 18.2)	1.4 (−8.1 to 10.9)
SDAI remission	12	6.9 (−2 to 15.7)	3.6 (−5.2 to 12.3)	7.5 (−1.5 to 16.6)
EULAR good response	24	4.4 (−4.1 to 12.8)	7.6 (−0.7 to 15.8)	0.4 (−8.4 to 9.2)
EULAR good response	12	7.3 (−1.3 to 16)	4.9 (−3.8 to 13.6)	10.4 (1.8 to 19.1)

ACR=American College of Rheumatology; CDAI=clinical disease activity index; DAS28=disease activity score of 28 joints (C reactive protein based, four variables); EULAR=European League Against Rheumatism; SDAI=simple disease activity index.

Primary analyses, intention-to-treat population, logistic regression analysis adjusted for baseline covariates. Marginal estimates averaged over the covariates as observed in the sample.

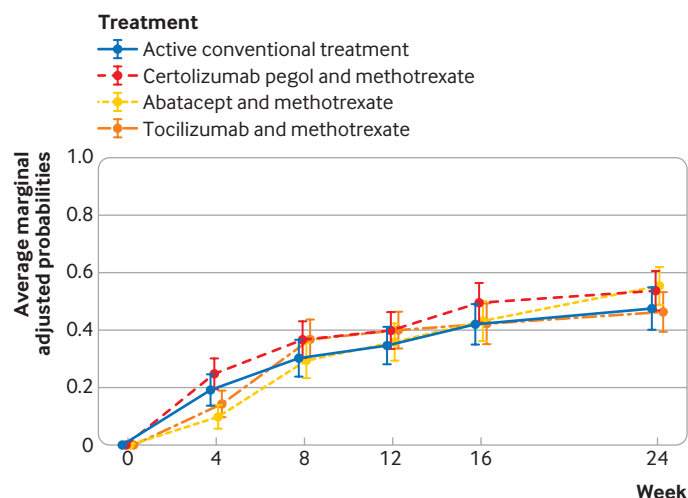


Fig 1 | Probability of clinical disease activity index (CDAI) remission over time for each treatment group. Longitudinal analysis on the intention-to-treat population using adjusted generalised estimating equations and accounting for within patient correlation. Average marginal estimates are shown, averaged over the covariates as observed in the sample. Bars indicate 95% confidence intervals

treatment in treatment naïve patients with rheumatoid arthritis, and includes three different biological drugs. We consider the generalisability of our findings to be high because 90% of screened patients underwent randomisation, and the baseline characteristics were typical for treatment naïve patients with poor prognosis.

One limitation is that, although this was a large investigator initiated study in patients with early rheumatoid arthritis, it was not powered to directly compare the biological drugs to each other. Another limitation is the open label design, which could influence the decision to proceed in the trial after randomisation. Only two patients (one in arm 1 and one in arm 4) withdrew informed consent after randomisation. The open label design, although partly offset by the use of blinded joint assessors, could influence certain subjective outcomes; expectation bias would probably have disfavoured the conventional treatment arm in this instance. Longer treatment follow-up is needed for cardiovascular events, corticosteroid

related safety outcomes, and structural damage; these will be assessed after 48 weeks.

Strengths and weaknesses in relation to other studies, discussing important differences in results

Our findings contrast with phase III trials that have consistently shown a minimum of 10-20% lower remission rates in the methotrexate alone arm.¹¹⁻¹³ Inspired by clinical practice (and in contrast to phase III trials), we used corticosteroids as bridging treatment because methotrexate is a slow acting drug. Some trials in treatment naïve patients with early rheumatoid arthritis have studied methotrexate combined with corticosteroids (orally or intra-articularly) as bridging treatment and shown good efficacy. However, these trials were without biological comparators, used biological treatment only as induction treatment, combined the biological comparator with corticosteroids, or used higher doses of corticosteroids and suboptimal doses of methotrexate.^{6 7 31-33}

In the EXXELERATE study of methotrexate, which included insufficient responders with established rheumatoid arthritis, two tumour necrosis factor inhibitors were compared (certolizumab pegol and adalimumab) and no differences in efficacy were found.³⁴ In the ORBIT trial,³⁵ rituximab was non-inferior to tumour necrosis factor inhibitors (adalimumab or etanercept) in patients who were seropositive and had early rheumatoid arthritis, and insufficient response to synthetic disease modifying drugs. In the ATTEST and AMPLE trials, abatacept was compared with infliximab (a tumour necrosis factor inhibitor) and adalimumab, respectively, in patients with inadequate response to methotrexate and the efficacy of abatacept was similar to that of the tumour necrosis factor inhibitor.^{36 37} In agreement with our findings, abatacept had fewer discontinuations owing to adverse events than adalimumab.³⁷

What the study adds in light of relevant systematic reviews and meta-analyses

A recent systematic review and network meta-analysis of methotrexate naïve patients mainly provided indirect comparisons of biologicals to each other.³⁸ The authors

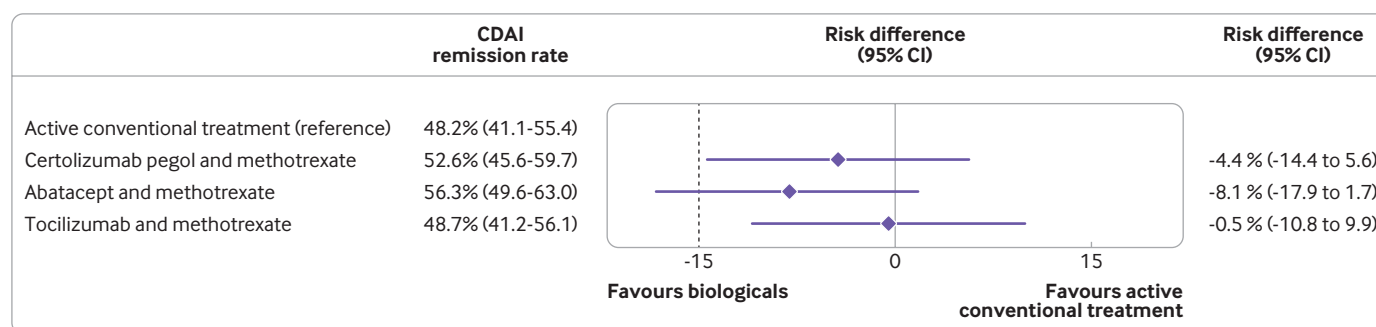


Fig 2 | Forest plot of risk differences. Estimated differences (95% confidence intervals) in clinical disease activity index (CDAI) remission rates at 24 weeks between active conventional treatment and methotrexate in combination with certolizumab pegol, abatacept, or tocilizumab. Logistic regression analysis, adjusted for sex, anti-citrullinated protein antibody positivity status, country, age, body mass index and baseline disease activity score of 28 joints (C reactive protein based, four variables; marginal estimates averaged over covariates as observed in sample). Dashed line shows non-inferiority margin. Figure based on per protocol dataset

Table 3 | Adverse events in the safety population at 24 weeks. Values are number of events (number of patients; percentage of patients in that arm who experienced at least one event)

Parameter	Active conventional treatment (n=197)	Certolizumab pegol and methotrexate (n=202)	Abatacept and methotrexate (n=204)	Tocilizumab and methotrexate (n=184)
Summary of adverse events				
Adverse events	562 (170; 86.3)	530 (167; 82.7)	527 (163; 79.9)	653 (175; 95.1)
Serious adverse events	13 (11; 5.6)	20 (17; 8.4)	10 (10; 4.9)	10 (9; 4.9)
Deaths	—	1 (1; 0.5)*	—	—
Adverse events of special interest†				
Infections	93 (68; 34.5)	103 (74; 36.6)	102 (70; 34.3)	126 (84; 45.7)
Cardiovascular disease	3 (3; 1.5)	8 (7; 3.5)	10 (9; 4.4)	6 (6; 3.3)
Cataract	3 (2; 1)	—	3 (2; 1)	—
Demyelinating disease	—	1 (1; 0.5)	—	—
Diabetes mellitus	2 (2; 1)	—	—	—
Herpes zoster	3 (3; 1.5)	1 (1; 0.5)	—	—
Malignancy	—	1 (1; 0.5)	2 (2; 1)	3 (3; 1.6)
Osteoporosis	1 (1; 0.5)	3 (3; 1.5)	—	1 (1; 0.5)
Weight gain	2 (2; 1)	—	1 (1; 0.5)	1 (1; 0.5)

Patients could have more than one category of events. Adverse events are summarised by the safety population, and by actual treatment (not as randomised). The 17 Finnish patients randomised to arm 4 (tocilizumab) but not receiving it owing to unavailability are not included.

*Sudden death in 78 year old woman. A lump in the breast was discovered at the screening visit, later breast cancer was diagnosed. She stopped treatment 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.

†No events were coded as venous thromboembolism and tuberculosis. Osteoporosis events were reported shortly after baseline, based on, for example, baseline dual energy x ray absorptiometry scan.

concluded that moderate quality evidence was found that, compared with methotrexate alone, biologicals given in combination with methotrexate were associated with absolute and relative clinically meaningful benefits (15%) in DAS28 remission rates, and no higher risk of serious adverse events existed compared with methotrexate. Other systematic reviews and network meta-analyses looking at the comparative effectiveness of biological drugs have mainly focused on patients with disease that has failed to respond to methotrexate.³⁹

Meaning of the study: possible explanations and implications for clinicians and policy makers

The primary clinical outcome was CDAI remission at 24 weeks, a more stringent remission criterion than the DAS28 based criterion, which has traditionally been used in many trials. We chose the CDAI because the algorithm does not include acute phase reactants, which are differentially impacted upon by different biological treatments.

National preferences on the exact implementation of active conventional treatment were reflected in slightly different strategies in Denmark and Finland (triple treatment with methotrexate, sulfasalazine, and hydroxychloroquine combined with intra-articular triamcinolone hexacetonide) versus Sweden, Norway, the Netherlands, and Iceland (methotrexate combined with 20 mg prednisolone initially, tapered to 5 mg after nine weeks and discontinued after nine months). The active conventional treatment strategy with bridging corticosteroid brought promising results until week 24; the clinical results at week 48 will inform us if this is sustainable in the long term.

Abatacept had fewest discontinuations, which contributed to its higher remission rate, because patients who stopped treatment early were imputed as non-responders. This finding emphasises the role of tolerability and harms in the evaluation of drug efficacy.

Unanswered questions and future research

The study is ongoing. Follow-up at 48 weeks will show long term efficacy, and structural damage and harms for each of the four treatments. The second part of the trial will assess and compare two alternative de-escalation strategies in patients who have achieved remission. Research projects based on the NORD-STAR biobank will inform us whether one or more of the biological drugs might be better tailored to different subgroups of patients.

Conclusion

High remission rates were found in disease modifying antirheumatic drug naïve patients with early rheumatoid arthritis who started treatment with methotrexate in combination with abatacept, certolizumab pegol, tocilizumab, or active conventional treatment. We observed higher CDAI remission rates for abatacept versus active conventional treatment, but not for certolizumab pegol or tocilizumab versus active conventional treatment. Other remission rates were similar across treatments. Non-inferiority analysis indicated that active conventional treatment was non-inferior to certolizumab pegol and tocilizumab, but not to abatacept. Rates of adverse events and early withdrawals were lowest for abatacept. The results highlight the efficacy and safety of active conventional treatment based on methotrexate combined with corticosteroids, with nominally better results for abatacept, in treatment naïve early rheumatoid arthritis.

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Data sharing: The authors commit to making the relevant anonymised patient level data available on reasonable request.

The lead author (MLH) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as originally planned have been explained.

Dissemination to participants and related patient and public communities: The patient organisations of the involved countries will be involved in the dissemination plans of this research. We plan to disseminate the results to study participants and to patient organisations as well as to the public through the media after publication.

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Web appendix: Supplementary appendix

Web appendix: Original protocol

Web appendix: Final protocol

Web appendix: Statistical analysis plan

Web appendix: Protocol amendments

Web appendix: Study sites