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

Merete Lund Hetland,1,2 Espen A Haavardsholm,3 Anna Rudin,4,5 Dan Nordstrøm,6,7 Michael Nurmohamed,8,9 Bjorn Gudbjornsson,10,11 Jon Lampa,12 Kim Hørslev-Petersen,13,14 Till Uhlig,3,15 Gerdur Grondal,10,11 Mikkel Østergaard,1,2 Marte S Heiberg,3 Jos Twisk,16 Kristina Lend,1,2 Simon Krabbe,1,2 Lise Hejl Hylstrup,1,2 Joakim Lindqvist,1,2 Anna-Karin Hultgård Ekwall,5,6 Kathrine Lederballe Grøn,3 Meliha Kapetanovic,17 Francesca Faustini,12 Riitta Tuompo,6,7 Tove Lorenzen,18 Giovanna Cagnotto,19,20 Eva Baekklund,21 Oliver Hendricks,13 Daisy Vedder,8 Tuulikki Sokka-Izler,22 Tomas Husmark,23 Maud-Kristine Aga Ljoså,24 Eli Brodin,25 Torkell Ellingsen,26 Annika Söderbergh,27 Milad Rizk,28 Åsa Reckner Olsson,29 Per Larsson,10 Line Uhrenholt,31 Søren Andreas Just,32 David John Stevens,33 Trine Bay Laurberg,34 Gunnstein Bakland,35 Inge C Olsen,36 Ronald van Vollenhoven,9,12 on behalf of the NORD-STAR study group.

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 naive 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 rates 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% (95% confidence interval 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 conventional treatment versus certolizumab pegol and tocilizumab, but not to abatacept.

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.

For numbered affiliations see end of the article.
Correspondence to:
M L Hetland
Copenhagen Center for Arthritis Research, Center for Rheumatology and Spine Diseases, Rigshospitalet, Valdemar Hansens Vej 17, DK-2600 Glostrup, Denmark,
merete.hetland@dadimnet.dk
(ORCID 0000-0003-4229-6818)
Additional material is published online only. To view please visit the journal online.
Cite this as: BMJ 2020;371:m4328
http://dx.doi.org/10.1136/bmj.m4328
Accepted: 19 August 2020

BMJ: first published as 10.1136/bmj.m4328 on 2 December 2020. Downloaded from http://www.bmj.com/ on 26 January 2021 at Linkopings Universitets Bibliotek. Protected by copyright.
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. 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 principal 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.

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. 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 tender joint counts, patient global score, and 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.
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) enterotables sulfasalazine (2 g/day) combined with hydroxychloroquine (35 mg/kg every week or 200 mg/day) and mandatory intra-articular tramcinolone hexacetinide 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. 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 CDAIs<2.8) at week 24. 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). 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 (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).

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 the 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
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 treatment.

---

**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 (12.3) | 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) |
| EULAR good response 12       | 12.7 (3.6)                         | 12.7 (3.6)                                   | 12.7 (3.6)                        | 12.7 (3.6)                        |
| EULAR good response 24       | 4.4 (1.1)                          | 4.4 (1.1)                                    | 4.4 (1.1)                         | 4.4 (1.1)                         |
| SDAI remission 12            | 25.8 (13.4)                        | 25.8 (13.4)                                  | 25.8 (13.4)                       | 25.8 (13.4)                       |
| SDAI remission 24            | 6.4 (2.3)                          | 6.4 (2.3)                                    | 6.4 (2.3)                         | 6.4 (2.3)                         |
| CRP=C reactive protein.      |                                    |                                              |                                   |                                    |

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

---

**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 vs active conventional treatment | Abatacept and methotrexate vs active conventional treatment | Tocilizumab and methotrexate vs active conventional treatment |
|----------------------------|---------|---------------------------------------------------------------------|----------------------------------------------------------|----------------------------------------------------------|
| **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 (−6.4 to 13.9)                                       | −3.8 (−13.2 to 5.6)                                      |
| DAS28 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)                                      |
| SDM remission              | 12      | 5.8 (−3.3 to 14.9)                                                  | 2.2 (−6.9 to 13.3)                                       | 14 (4.8 to 23.1)                                        |
| SDM remission              | 24      | 6.4 (−3 to 15.7)                                                    | 8.9 (−0.3 to 18.2)                                       | 1.4 (−8.1 to 10.9)                                      |
| EULAR good response        | 12      | 3.3 (−1.3 to 16)                                                    | 3.3 (−1.3 to 16)                                        | 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.
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...
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.

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 naive early rheumatoid arthritis.

AUTHOR AFFILIATIONS

1Copenhagen Center for Arthritis Research (COPECARE) and DANBIO, Center for Rheumatology and Spine Diseases, Rigshospitalet, Glostrup, Denmark
2Department of Clinical Medicine, Faculty of Health Sciences, University of Copenhagen, Copenhagen, Denmark
3Department of Rheumatology, Diakonhjemmet Hospital, Oslo, Norway
4Rheumatology Clinic, Sahlgrenska University Hospital, Gothenburg, Sweden

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) |
|-----------|--------------------------------------|---------------------------------------------|------------------------------------|------------------------------------|
| 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.

†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.

*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.

© BMJ Publishing Group Ltd 2020. All rights reserved. See permissions for more details. This is an Open Access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/
Inger Marie Jensen Hansen, Jarno Rutanen, Jens Nathann, Johan Back, Johan Wallman, Johanna Carlstedt, Jon Einarsson, Jorgen Lysholt, Kajsa Oberg, Karatina Almehed, Kati Mykkänen, Lena Karlberg, Malin Hemborg, Maria K Stilling-Vinther, Marjatta Leirisalo-Rapo, Mohamed Hamede, Nancy Vivar, Olli Kaipainen-Seppanen, Peter Olsson, Petrus Linge, Pia Lindell, Pia Neuer Jensen, Pinja Parmarine, René Obstgärd, Sabine Dieperink, Sarah Nyom Christensen, Sofia Exarchou, Thib Salet, Tor Olafsson, Trude Bruun, Vappu Rantalaiho, Yuva Borgas.

Contributors: MLH, EAH, DN, BG, KHP, TU, GG, MJ, RV designed the study and wrote the protocol. RV, DN, MSK, EAH, Niels Steen Krogh, DG, SK, MLH developed the CRFs. MLH, EAH, AR, DN, MN, BG, JL, KHP, TU, GG, MG, MSK, SJ, KL, AKHE, KLG, MK, FT, RT, TL, GC, FBA, OH, DV, TSI, TH, MKAL, EBR, TE, AS, MR, ARO, PL, TI, SAI, DJS, TBI, GB, RV contributed to the data collection and data cleaning. SK and Niels Steen Krogh did data management. JT and ICO conducted the statistical analyses. ICO and SK made the figures. MLH 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. MLH and RV 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.

Funding: Funding was obtained through public sources: Academy of Finland (grant No 258536), Finnish Lakareallianskapet, grant from the South-Eastern Health Region, Norway, HUCH Institutional grant, Finland (grant No 11 59001), Icelandic Society for Rheumatology, interregional grant from all health regions in Norway, Nordforsk (grant No 70945), Regionernes Medicinpulje, Denmark (grant No 14/217), Stockholm County Council, Sweden (grant No 20100490), Swedish Medical Research Council (grant No C0634901, D0342301, 2015-00891_1_S), Swedish Rheumatism Association, The Research Fund of University Hospital, Rekyjavik, Iceland (A2015017). UCBD supported the work in the context of an investigator initiated study where UCB provided certolizumab pegol at no cost. UCB 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. Bristol-Myers Squibb (BMS) provided abatacept at no cost. In addition, the Karolinska Institute received several unrestricted grants from BMS; these were subsequently transferred to the principal investigators of Denmark, Finland, and the Netherlands to help defray various trial related costs at the local level. BMS 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. The final manuscript was provided for courtesy review to UCB and BMS in line with Good Publication Practice (GPP3). We confirm the independence of researchers from funders and that all authors, external and internal, had full access to all of the data (including statistical reports and tables) in the study and can take responsibility of the integrity of the data and the accuracy of the data analysis.

Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: support from Academy of Finland, Finnish Lakareallianskapet, South-Eastern Health Region (Norway), HUCH (Finland), Icelandic Society for Rheumatology, all health regions in Norway, Nordforsk, Regionernes Medicinpulje (Denmark), Stockholm County Council (Sweden), Swedish Medical Research Council, Swedish Rheumatism Association, The Research Fund of University Hospital (Rekyjavik, Iceland) for the submitted work; MLH reports grants from Nordforsk, from Danske Regioner during the conduct of the study; grants from Bristol-Myers Squibb, grants from AbbVie, grants from Roche, grants from Novartis, grants and personal fees from Merck, grants and personal fees from Biogen, grants and personal fees from Pfizer, personal fees from Eli Lilly, personal fees from Oron Pharma, personal fees from CellTrion, personal fees from Samsung Bioepsi, personal fees from Janssen Biologics BV, personal fees from MSD, outside the submitted work; she chairs the steering committee of the Danish Rheumatology Quality Registry (DANBIO), which receives public funding from the hospital owners and funding from pharmaceautical companies; EAH reports grants from NordForsk, grants from the Norwegian Regional Health Authorities, grants from the South-Eastern Norway Regional Health Authority, during the conduct of the study, personal fees from Pfizer, personal fees from AbbVie, personal fees from Celgene, personal fees from Novartis, personal fees from Janssen, personal fees from Gilead, personal fees from Eli-Lilly, personal fees from UCB, outside the submitted work; AR reports grants from the Swedish Research Council, financial support from AstraZeneca, outside the submitted work; DN reports from
UCB, grants from BMS, during the conduct of the study; grants from AbbVie, grants from Celgene, grants from MSD, grants from Novartis, grants from Pfizer from the outside submitted work; MN reports grants from BMS, during the conduct of the study; grants from AbbVie, grants from BMS, personal fees from Celtrion, grants from MSD, grants from Pfizer, personal fees from Eli Lilly, grants from Ajang, outside the submitted work; BG reports personal fees from varitis, outside the submitted work; TU reports a grant from NORDFORSK during the conduct of the study, personal fees from Grünenthal, personal fees from Lilly, personal fees from Novartis, personal fees from Pfizer, outside the submitted work; MB reports grants, personal fees and non-financial support from AbbVie, grants, personal fees and non-financial support from BMS, personal fees from Boehringer-Ingelheim, personal fees from Eli Lilly, personal fees and non-financial support from Janssen, personal fees and non-financial support from Merck, personal fees and non-financial support from Pfizer, personal fees and non-financial support from Roche, personal fees and non-financial support from UCB, grants and personal fees from Celgene, personal fees from Sanofi, personal fees from Regeneron, grants, personal fees and non-financial support from Novartis, personal fees from Orion, personal fees from Hospira, outside the submitted work; MSH reports grants from the South-Eastern Norway Regional Health Authority, during the conduct of the study, personal fees from Lilly, outside the submitted work; SK reports receiving grants from AbbVie, MSD and Novartis outside the submitted work; AKHE reports receiving personal fees from AbbVie, personal fees from Pfizer, outside the submitted work; KLG reports grants from BMS, outside the submitted work; RT reports grants from Finnish Rheumatology Research Fund, during the conduct of the study; OH reports non-financial support from Pfizer, personal fees from AbbVie, personal fees from Novartis, during the conduct of the study; TS reports non-financial support from DiaGraphIT, personal fees from AbbVie, personal fees from BMS, personal fees from Celgene, personal fees from Medac, personal fees from Merck, personal fees from Novartis, personal fees from Onon Pharma, personal fees from Pfizer, personal fees from Roche, personal fees from Sandoz, personal fees from UCB, personal fees from Boehringer Ingelheim, outside the submitted work; LJ reports personal fees from AbbVie, Eli Lilly and Novartis (speaker fees), outside the submitted work; DJJ reports grants from KLINFORSK, during the conduct of the study; TBL reports personal fees from UCB, outside the submitted work; GB reports personal fees from BMS, outside the submitted work; ABA reports personal fees from AbbVie, personal fees from Eli Lilly, personal fees from Novartis, personal fees from Pfizer, outside the submitted work; AB reports grants from BMS, during the conduct of the study. CT reports grants and personal fees from Bristol Myers-Squibb, personal fees from Roche, personal fees from AbbVie, personal fees from Pfizer, outside the submitted work; HR reports personal fees from MSD, personal fees from Roche, personal fees from AbbVie, personal fees from Celgene, outside the submitted work; JR reports grants from BMS, during the conduct of the study, JR reports fees from Celgene, fees from Eli Lilly, fees from Novartis, outside the submitted work; KM reports personal fees from AbbVie, personal fees from Celgene, personal fees from Medac, personal fees from BMS, outside the submitted work; OKS reports grants from the Research Committee of the Kuopio University Hospital Catchment Area for the State Research Funding, during the conduct of the study, non-financial support from Pfizer, non-financial support from Novartis, non-financial support from MSD, personal fees from Boehringer Ingelheim, outside the submitted work; PP reports personal fees from Novartis Finland Oy, outside the submitted work; KP reports personal fees from Bristol-Meyer Squibb, personal fees and non-financial support from AbbVie, personal fees from Gilead, personal fees from Janssen, personal fees from Eli Lilly, personal fees from Novartis, outside the submitted work; SN reports personal fees from Bristol Myers-Squibb, personal fees from General Electric, outside the submitted work; SE reports personal fees from Novartis, outside the submitted work; TO reports personal fees from Eli Lilly, consultancy fee from Merck Sharp and Dohme, outside the submitted work; reports grants from BMS, during the conduct of the study, grants from Roche, grants from Mylan, other from AbbVie, outside the submitted work; VR reports grants from BMS, during the conduct of the study, grants from Roche, grants from Mylan, other from AbbVie, outside the submitted work; RV reports grants from BMS, during the conduct of the study; grants from GSK, Lilly, UCB, grants from Pfizer, Roche, personal fees from AbbVie, AstraZeneca, Biogen, Biotech, Celgene, Galapagos, Gilead, Janssen, Pfizer, Servier, UCB, outside the submitted work; no other relationships or activities that could appear to have influenced the submitted work.

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/A (Sweden); Den Nationale Komité for Region Hovedstaden, ID: H-2-2013-153 (Denmark); Regional committees for medical research ethics, ID: 2014/2191REC 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 Stotervaartziekenhuis in Reade, ID: NL06775.048.17 (The Netherlands); The National Biobank of Denmark (DK), ID: 13-300/1515 (Denmark); The patients provided written informed consent before any study-related procedures.

Data sharing: The authors commit to making the relevant anonymised patient level data available on request. To obtain the data, investigators should contact the corresponding author via email. 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.

Provenance and peer review: Not commissioned, externally peer reviewed.

This is an Open Access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/.

1 Smolen JS, Aletaha D, McInnes IB. Rheumatoid arthritis. Lancet 2016;388:2023-38. doi:10.1016/S0140-6736(16)30173-8
2 Klarenkog L, Catrina AI, Paget S. Rheumatoid arthritis. Lancet 2009;373:659-72. doi:10.1016/S0140-6736(09)60008-8
3 Emery P, Salomon M. Early rheumatoid arthritis: time to aim for remission? Ann Rheum Dis 1995;54:944-7. doi:10.1136/ard.54.12.944
4 Smolen JS, Landewe RBM, Bijlsma JWJ, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological modifying antirheumatic drugs: 2019 update. Ann Rheum Dis 2020;79:685-699. doi:10.1136/annrheumdis-2019-216655
5 Singh JA, Saag KG, Bridges SL, et al. 2015 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis. Arthritis Care Res (Hoboken) 2016;68:1096-1123. doi:10.1002/art.39315
6 Hetland ML, Stengaard-Pedersen K, Junker P, et al. Combination treatment with methotrexate, cyclosporine, and intraarticular betamethasone compared with methotrexate and intraarticular betamethasone in early active rheumatoid arthritis: an investigator-initiated, multicenter, randomized, double-blind, par. Arthritis Rheum 2006;54:1401-9. doi:10.1002/art.21796
7 Goekeop-Ruiteman YPM, de Vries-Bouwstra JK, Allaart CF, et al. Clinical and radiographic outcomes of four different treatment strategies in patients with early rheumatoid arthritis the BeSt Study: a randomized controlled trial. Arthritis Rheum 2005;52:3381-90.
8 Wassenberg S, Rau R, Steinfeld P, Zeidler H. Very low-dose prednisolone in early rheumatoid arthritis retards radiographic progression over two years: a multicenter, double-blind, placebo-controlled trial. Arthritis Rheum 2005;52:3371-80. doi:10.1002/art.21421
9 St Clair EW, Van der Heijde DMF, Smolen JS, et al. Combination of infliximab and methotrexate therapy for early rheumatoid arthritis: a randomized, controlled trial. Arthritis Rheum 2004;50:3432-43. doi:10.1002/art.20568
10 Breederveld FC, Weisman MH, Kavanaugh AF, et al. The PREMIER study: a multicenter, randomized, double-blind clinical trial of combination therapy with adalimumab plus methotrexate versus methotrexate alone or adalimumab alone in patients with early, aggressive rheumatoid arthritis who had not had prior treatment. Arthritis Rheum 2006;54:26-37. doi:10.1002/art.21119
11 Westhovens R, Robles M, Ximenes AC, et al. Clinical efficacy and safety of abatacept in methotrexate-naive patients with early rheumatoid arthritis and poor prognostic factors. Ann Rheum Dis 2009;68:1870-7. doi:10.1136/ard.2008.101121
12 Bijlsma JW, Welsing PM, Woodworth TG, et al. Early rheumatoid arthritis treated with tocilizumab, methotrexate, or their combination (U-Act-Early): a multicentre, randomised, double-blind, double-dummy, strategy trial. Lancet 2016;388:343-55. doi:10.1016/S0140-6736(16)30136-4
Emery P, Bingham CO, Burmester GR, et al. Certolizumab pegol in combination with dose-optimised methotrexate in DMARD-naive patients with early, active rheumatoid arthritis with poor prognostic factors: 1-year results from C EARLY, a randomised, double-blind, placebo-controlled phase III study. Ann Rheum Dis 2017; 76:96-104. doi:10.1136/annrheumdis-2015-209057

Glinatsi D, Heiberg MS, Rudin A, et al. Head-to-head comparison of aggressive conventional therapy and three biological treatments and comparison of two de-escalation strategies in patients who respond to treatment: study protocol for a multicenter, randomised, open-label, blinded-assessor, pha. Trials 2017;18:161. doi:10.1186/s13063-017-1891-x

Schulz HF, Altman DG, Moher D. CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials. BMJ. 2010. www.consort-statement.org

Juszczak E, Altman DG, Hopewell S, Schulz K. Reporting of multi-arm parallel-group randomised trials: extension of the CONSORT 2010 statement. JAMA 2019;321:16. doi:10.1001/jama.2019.3087

Moher D, Hopewell S, Schulz KF, et al. CONSORT 2010 explanation and elaboration: updated guidelines for reporting parallel group randomised trials. BMJ. 2010;340:c669. doi:10.1136/bmj.c669

Aletaha D, Neogi T, Silman AJ, et al. 2010 Rheumatoid arthritis classification criteria: An American College of Rheumatology/European League Against Rheumatism collaborative initiative. Arthritis Rheum 2010;62:2569-81. doi:10.1002/art.2758

Aletaha D, Martinez-Avila J, Kivin TK, Smolen JS. Definition of treatment response in rheumatoid arthritis based on the simplified and the clinical disease activity index. Ann Rheum Dis 2012;71:1190-6. doi:10.1136/annrheumdis-2012-201491

Felson DT, Smolen JS, Wells G, et al. American College of Rheumatology/European League Against Rheumatism provisional definition of remission in rheumatoid arthritis for clinical trials. Arthritis Rheum 2011;63:573-86. doi:10.1002/art.30129

Fransen J, Cremerens MCW, Van Riel PLCM. Remission in rheumatoid arthritis: agreement of the disease activity score (DAS28) with the ARA preliminary remission criteria. Rheumatology (Oxford) 2004;43:1252-5. doi:10.1093/rheumatology/keh297

Aletaha D, Ward MM, Machold KP, Nell VPK, Smolen JS. Remission and active disease in rheumatoid arthritis defining criteria for disease activity states. Arthritis Rheum 2005;52:2625-36. doi:10.1002/art.21235

van Gestel AM, Haagsma CJ, Van Riel PLCM. Validation of rheumatoid arthritis improvement criteria that include simplified joint counts. Arthritis Rheum 1998;41:1845-50.1002/1529-0131(199810)41: doi:10.1002/1529-0131(199810)41:0131:1845:1845;2.k

van Vollenhoven RF, Ernestam S, Geborek P, et al. Addition of infliximab compared with addition of sulfasalazine and hydroxychloroquine to methotrexate in patients with early rheumatoid arthritis (Swefot trial): 1-year results of a randomised trial. Lancet 2009;374:459-66. doi:10.1016/S0140-6736(09)60944-2

Emery P, Breedveld FC, Hall S, et al. Comparison of methotrexate monotherapy with a combination of methotrexate and etanercept in active, early, moderate to severe rheumatoid arthritis (COMET): a randomised, double-blind, parallel treatment trial. Lancet 2007;372:375-82. doi:10.1016/S0140-6736(07)61000-4

Moreland LW, O’Dell JR, Paulus HE, Curtis JR, Bathon JM, St Clair EW, et al. A randomized comparative effectiveness study of oral triple therapy versus etanercept plus methotrexate in early aggressive rheumatoid arthritis trial. Arthritis Rheum 2012;64:2826-35. doi:10.1002/art.34498

Sokka T, Heitland ML, Maksinen H, et al. Remission and rheumatoid arthritis data on patients receiving usual care in twenty-two countries. Arthritis Rheum 2008;58:2642-51. doi:10.1002/art.23794

Emery P, Keystone E, Tony HP, et al. IL-6 receptor inhibition with tocilizumab improves treatment outcomes in patients with rheumatoid arthritis refractory to anti-tumour necrosis factor biologicals: results from a 24-week multicentre randomised placebo-controlled trial. Ann Rheum Dis 2008;67:1516-23. doi:10.1136/ard.2008.092932

Yoo DH, Hyrcay P, Miranda P, et al. A randomised, double-blind, parallel-group study to demonstrate equivalence in efficacy and safety of CT-P13 compared with innovator infliximab when coadministered with methotrexate in patients with active rheumatoid arthritis: the PLANETRA study. Ann Rheum Dis 2013;72:1613-20. doi:10.1136/annrheumdis-2012-203990

Jørgensen KK, Olsen E, Goll GL, et al. Switching from originator infliximab to biosimilar CT-P13 compared with maintained treatment with originator infliximab (NOR-SWITCH): a 52-week, randomised, double-blind, non-inferiority trial. Lancet 2017;389:2304-16. doi:10.1016/S0140-6736(17)30668-5

Harslev-Petersen K, Hetland ML, Jumper P, et al. Adalimumab added as a treat-to-target strategy with methotrexate and intra-articular triamcinolone in early rheumatoid arthritis increased remission rates, function and quality of life. The OPERA Study: an investigator-initiated, randomised, double-blind. Ann Rheum Dis 2014;73:654-61. doi:10.1136/annrheumdis-2012-207275

de Jong PH, Hazes JM, Han HK, et al. Randomised comparison of initial triple DMARD therapy with methotrexate monotherapy in combination with low-dose glucocorticoid bridging therapy: 1-year data of the DREACH trial. Ann Rheum Dis 2014;73:1313-9. doi:10.1136/annrheumdis-2013-204788

Verschuuren P, De Cock D, Corly L, et al. Methotrexate in combination with other DMARDs is not superior to methotrexate alone for remission induction with moderate-to-high-dose glucocorticoid bridging in early rheumatoid arthritis after 16 weeks of treatment: the CareERA study. Ann Rheum Dis 2015;74:27-34. doi:10.1136/annrheumdis-2014-204589

Smolen JS, Burmester G, Combe B, et al. Head-to-head comparison of certolizumab pegol versus adalimumab in rheumatoid arthritis: 2-year effi cacy and safety results from the randomised EXCELLETER study. Lancet 2016;388:2763-74. doi:10.1016/S0140-6736(16)31651-8

Porter D, Van Melckebeke J, Dale J, et al. Tumour necrosis factor inhibition versus rituximab for patients with rheumatoid arthritis who require biological treatment (ORBIT): an open-label, randomised controlled, non-inferiority, trial. Lancet 2016;388:239-47. doi:10.1016/S0140-6736(16)31650-9

Schiff M, Keiserman M, Coding C, et al. Efficacy and safety of abatacept or infliximab vs placebo in ATTENTION: a phase III, multicentre, randomised, double-blind, placebo-controlled study in patients with rheumatoid arthritis and an inadequate response to methotrexate. Ann Rheum Dis 2008;67:1096-103. doi:10.1136/annrheumdis-2007-080002

Schiff M, Weinblatt ME, Valente R, et al. Head-to-head comparison of subcutaneous abatacept versus adalimumab for rheumatoid arthritis: two-year efficacy and safety findings from AMPLIFY trial. Ann Rheum Dis 2014;73:86-94. doi:10.1136/annrheumdis-2013-203843

Singh JA, Hossain A, Mudano A, Tanjong Ghogomu E, Suarez-Almazor M, Buchbinder R, et al. Biologics or tocilizumab for people with rheumatoid arthritis naive to methotrexate: a systematic review and network meta-analysis (Review). Cochrane Database Syst Rev 2017,5

Junk K, Biester K, Krause D, et al. Comparative effectiveness of biological medicines in rheumatoid arthritis: Systematic review and network meta-analysis including aggregate results from realanalysed individual patient data. BMJ 2020;370:1-11

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