Head-to-head comparison of certolizumab pegol versus adalimumab in rheumatoid arthritis: 2-year efficacy and safety results from the randomised EXXELERATE study

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Summary

Background To date, head-to-head trials comparing the efficacy and safety of biological disease-modifying antirheumatic drugs within the same class, including TNF inhibitors, in patients with active rheumatoid arthritis despite methotrexate therapy are lacking. We aimed to compare the efficacy and safety of two different TNF inhibitors and to assess the efficacy and safety of switching to the other TNF inhibitor without a washout period after insufficient primary response to the first TNF inhibitor at week 12.

Methods In this 104-week, randomised, single-blind (double-blind until week 12 and investigator blind thereafter), parallel-group, head-to-head superiority study (EXXELERATE), eligible patients from 151 centres worldwide were aged 18 years or older with a diagnosis of rheumatoid arthritis at screening, as defined by the 2010 ACR/EULAR criteria, and had prognostic factors for severe disease progression, including a positive rheumatoid factor, or anti-cyclic citrullinated peptide antibody result, or both. Participants were randomly assigned (1:1) via an interactive voice and web response system with no stratification to receive certolizumab pegol plus methotrexate or adalimumab plus methotrexate. All study staff were kept masked throughout the study and participants were masked until week 12. At week 12, patients were classified as responders (by either achieving low disease activity [LDA] according to Disease Activity Score 28-erythrocyte sedimentation rate [DAS28-ESR] ≤3·2 or DAS28-ESR reduction ≥1·2 from baseline) or as non-responders. Non-responders to the first TNF inhibitor to which they were randomised were switched to the other TNF inhibitor with no washout period. Primary endpoints were the percentage of patients achieving a 20% improvement according to the American College of Rheumatology criteria (ACR20) at week 12 and LDA at week 104 (week 12 non-responders were considered LDA non-responders). This study is registered with ClinicalTrials.gov, number NCT01500278.

Findings Between Dec 14, 2011, and Nov 11, 2013, 1488 patients were screened of whom 915 were randomly assigned; 457 to certolizumab pegol plus methotrexate and 458 to adalimumab plus methotrexate. No statistically significant difference was observed in ACR20 response at week 12 (314 [69%] of 454 patients and 324 [71%] of 454 patients; odds ratio [OR] 0·90 [95% CI 0·67–1·20]; p=0·467) or DAS28-ESR LDA at week 104 (161 [35%] of 454 patients and 152 [33%] of 454 patients; OR 1·09 [0·82–1·45]; p=0·532) between certolizumab pegol plus methotrexate and adalimumab plus methotrexate, respectively. At week 12, 65 non-responders to certolizumab pegol were switched to adalimumab and 57 non-responders to adalimumab were switched to certolizumab pegol; 33 (58%) of 57 patients switching to certolizumab pegol and 40 (62%) of 65 patients switching to adalimumab responded 12 weeks later by achieving LDA or a DAS28-ESR reduction 1·2 or greater. 389 [75%] of 516 patients who received certolizumab pegol plus methotrexate and 386 [74%] of 523 patients who received adalimumab plus methotrexate reported treatment-emergent adverse events. Three deaths (1%) occurred in each group. No serious infection events were reported in the 70-day period after treatment switch.

Interpretation These results show that certolizumab pegol plus methotrexate is not superior to adalimumab plus methotrexate. The data also show the clinical benefit and safety of switching to a second TNF inhibitor without a washout period after primary failure to a first TNF inhibitor.

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Introduction

Rheumatoid arthritis is a chronic inflammatory disease driven by various proinflammatory cytokines.[1] Several biological disease-modifying anti-rheumatic drugs (bDMARDS) with different mechanisms of action, have been shown to be efficacious in the treatment of patients with rheumatoid arthritis.[1,2] Current treatment guidelines recommend escalating therapy to a combination of bDMARDs and methotrexate for patients with rheumatoid arthritis who have an inadequate response to conventional synthetic DMARDs (csDMARDs).[3,4] Indirect evidence from meta-analyses and direct evidence from a small number of head-to-head studies comparing TNF inhibitors to drugs with other mechanisms of action

Research in context

Evidence before this study

In 2010, before this study was initiated, a systematic literature review was done using search terms: anti-tumour necrosis factor (TNF), certolizumab pegol, infliximab, adalimumab, etanercept, golimumab, direct comparison, efficacy, and safety in the Ovid and PubMed database platforms. The results of this systematic literature review confirmed that no randomised controlled trials had directly compared the efficacy and safety of two TNF inhibitors. Therapy options for rheumatoid arthritis have progressed rapidly in recent years with the introduction of biological disease-modifying antirheumatic drugs (bDMARDs). EULAR and ACR recommendations for the management of rheumatoid arthritis suggest first treating patients with a conventional synthetic DMARD. If an adequate response is not achieved, it is then recommended to add a bDMARD. The TNF inhibitor class of bDMARD is often the first class of bDMARDs used. EULAR and ACR guidelines recommend switching patients to another TNF inhibitor or to a bDMARD with a different mechanism of action if they fail to respond to their first bDMARD by 3 months. To date, no direct head-to-head trials have compared the efficacy and safety of different TNF inhibitors. Furthermore, no studies have investigated the efficacy and safety of directly switching to a second TNF inhibitor following an inadequate response to the first TNF inhibitor. Evidence for the efficacy of switching from one TNF inhibitor to another has come from studies recruiting patients with a history of inadequate response to either primary or secondary treatment with a TNF inhibitor, for example the REALISTIC and GO-AFTER trials.

Added value of this study

In the absence of well-controlled clinical trial data, guidelines rely on indirect evidence from registries and meta-analyses. To the best of our knowledge, the EXXELERATE study is the first trial to compare two TNF inhibitors (certolizumab pegol and adalimumab) in a head-to-head setting and to assess the efficacy and safety of directly switching from one TNF inhibitor to another without a washout period following inadequate response to primary treatment with a TNF inhibitor.

Implications of all the available evidence

The results from EXXELERATE show, in a head-to-head setting, no significant difference between certolizumab pegol and adalimumab in combination with methotrexate in either short-term (12-week) or long-term (2-year) efficacy, and provide evidence supporting an initial treat-to-target principle, emphasising the importance of clinical decision making at week 12. By following this approach and using a second TNF inhibitor at week 12 (after an inadequate response to the first TNF inhibitor), clinicians can maximise, in a timely manner, the potential benefit of TNF inhibitor therapy for a patient. This also allows early identification of TNF inhibitor inadequate responder patients (within 6 months) who might potentially benefit from treatment that uses a different mechanism of action. Furthermore, EXXELERATE provides clinical evidence of comparable safety over 2 years between certolizumab pegol and adalimumab. Overall, these results support the use of TNF inhibitors in a methotrexate inadequate responder patient population and provide additional clinical evidence of the efficacy and safety of an immediate switch to a second TNF inhibitor in a primary TNF inhibitor inadequate responder population.

suggest that, on average, bDMARDs might be generally similar to one another in terms of efficacy and safety.[5–8] At present, the TNF inhibitors class of therapeutics are often the first biologics prescribed in clinical practice; however, a direct comparison of different TNF inhibitors has never been done. Direct head-to-head comparisons should provide the most rigorous evidence on the comparative effectiveness of different treatments.[5–7,9,10] In the absence of data from direct head-to-head trials, different TNF inhibitors can only be indirectly compared, which is difficult given several limitations with methods.[10,11]

In addition to selecting the optimal first-line drug, current treatment guidelines for rheumatoid arthritis recommend switching patients to an alternative therapy if they have inadequate improvement by 3 months after the start of treatment (defined as not achieving a reduction of Disease Activity Score 28-erythrocyte sedimentation rate [DAS28-ESR] ≥1·2 or a >50% improvement in Clinical Disease Activity Index [CDAI] or Simplified Disease Activity Index [SDAI]),[8,12] or they do not achieve the treatment target (preferably remission or low disease activity [LDA], which is appropriate for patients with refractory disease) by 6 months.[3,4,13] According to current American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) treatment recommendations,[3,4] patients who do not adequately respond to treatment with a first TNF inhibitor can switch to another TNF inhibitor or to a bDMARD with a different mechanism of action. There are five TNF inhibitors available for the treatment of rheumatoid arthritis: adalimumab, certolizumab pegol, etanercept, golimumab, and infliximab. Results from the REALISTIC[14] and GO-AFTER[15] studies which enrolled inadequate responders to TNF inhibitors, suggest that using a second TNF inhibitor has at least some clinical benefit in this refractory patient population. However, the patients in these studies, as in studies of other mechanisms of action in inadequate-responder to TNF inhibitor populations, comprised a heterogeneous patient population, who had been treated with different TNF inhibitors for different durations, had different reasons for discontinuation, included both primary and

secondary failures, and had inconsistent time periods between treatment with the previous TNF inhibitor and the new bDMARD.

We aimed to compare the efficacy and safety of two different TNF inhibitors and also to assess the efficacy and safety of switching to the other TNF inhibitor without a washout period, following insufficient response to the first TNF inhibitor at week 12. The study compared certolizumab pegol (a PEGylated, humanised, recombinant Fab′ fragment with one TNF binding site[16]) in combination with methotrexate with adalimumab (a human monoclonal antibody with two TNF binding sites) in combination with methotrexate in patients who previously did not respond to methotrexate therapy.

Methods

Study design and participants

EXXELERATE (NCT01500278) was a 104-week (2-year) randomised, single-blind (double blind until week 12 and investigator blind thereafter), parallel-group, head-to-head superiority study comparing certolizumab pegol with adalimumab, both with background methotrexate (figure 1A). The study was done at 175 centres (of which 151 recruited patients) in Europe (Austria, Bulgaria, Czech Republic, France, Germany, Hungary, Ireland, Italy, Poland, Portugal, Romania, Spain, and Switzerland) Australia, and North America (Canada, Mexico, and the USA).

Eligible patients were aged 18 years or older with a diagnosis of rheumatoid arthritis at screening, as defined by the 2010 ACR/EULAR criteria,[17] and had prognostic factors for severe disease progression, including a positive rheumatoid factor, or anti-cyclic citrullinated peptide antibody (ACPA) result, or both. Patients had active rheumatoid arthritis, defined as: DAS28-ESR higher than 3·2, four or more swollen joints (out of 28), and increased acute phase reactants (hsCRP ≥10 mg/L [normal range 0–3 mg/L], or ESR ≥28 mm/h, or both) at screening and baseline.

Patients were bDMARD-naive and with active disease despite a minimum 12-week course of methotrexate therapy prior to the screening visit, including a minimum of at least 28 days of stable dose methotrexate (15–25 mg per week orally or subcutaneously) before baseline. Stable doses of NSAIDs and oral glucocorticoids (≤10 mg/day prednisolone equivalent) were allowed, if the regimen was stable for the 7 and 28 days prior to baseline, respectively.

Patient exclusion criteria included, but were not limited to, serious infections within 12 months prior to baseline, active or ongoing tuberculosis infection, any history of congestive heart failure, demyelinating disorders, active malignancy or a history of cancer (≤2 episodes of basal cell carcinoma, or cervical carcinoma in situ that occurred >5 years prior to baseline were allowed). Patients were tested for tuberculosis before entering into the study, at week 52, and at week 104 using the QuantiFERON-TB GOLD In-Tube test (Quest Diagnostics, Madison, NJ, USA). Patients were excluded if they were treated with sulfasalazine or hydroxychloroquine within 28 days prior to baseline, or if they had a blood plasma leflunomide concentration >0·02 mg/L.

All patients provided written informed consent. The study protocol was reviewed by national or regional bodies, an independent ethics committee, or an institutional review board. This study was done in accordance with the ICH-Good Clinical Practice requirements and the principle of the Declaration of Helsinki, and the local laws of the countries involved.

Randomisation and masking

Patients were randomly assigned (1:1), with no stratification, to certolizumab pegol (400 mg weeks 0, 2, and 4, then 200 mg once every 2 weeks) plus methotrexate or adalimumab (40 mg once every 2 weeks) plus methotrexate via an interactive voice and web response system (IXRS, Almac, Craigavon, UK). All study staff were blinded to the treatment assignment throughout the study (including treatment switch) with the exception of the pharmacovigilance staff reporting serious adverse events, study drug dispensers, IXRS provider, and laboratory staff analysing plasma samples. Patients were blinded to treatment from baseline through week 12.

During the first 12 weeks of the trial, patients receiving adalimumab were also administered placebo injections at weeks 0, 2, and 4 to maintain blinding during the administration of the loading dose of certolizumab pegol. Both adalimumab and adalimumab placebo were delivered in a prefilled syringe labelled with an identification number and were administered to the patient by qualified, designated unblinded site personnel.

Procedures

At week 12, patients were classified as responders (defined as patients achieving either a DAS28-ESR ≤3·2 or a DAS28-ESR reduction from baseline of ≥1·2) or as non-responders (ie, those not meeting either response criteria). Week 12 responders continued the treatment they were originally randomised to at baseline until week 104. Week 12 non-responders randomised to the certolizumab pegol treatment group were immediately switched to receive adalimumab 40 mg once every 2 weeks plus methotrexate. Week 12 non-responders randomised to the adalimumab treatment group were immediately switched to receive certolizumab pegol 400 mg at weeks 12, 14, and 16 (loading dose), followed by certolizumab pegol 200 mg once every 2 weeks. Week 12 non-responder patients who were switched and were also non-responders at week 24 (ie, those not achieving DAS28-ESR ≤3·2 nor a DAS28-ESR reduction from week 12 of ≥1·2) were classified as TNFi non-responders and were withdrawn from the study.

All patients continued unblinded methotrexate at 15–25 mg per week (for toxicity or tolerability issues the

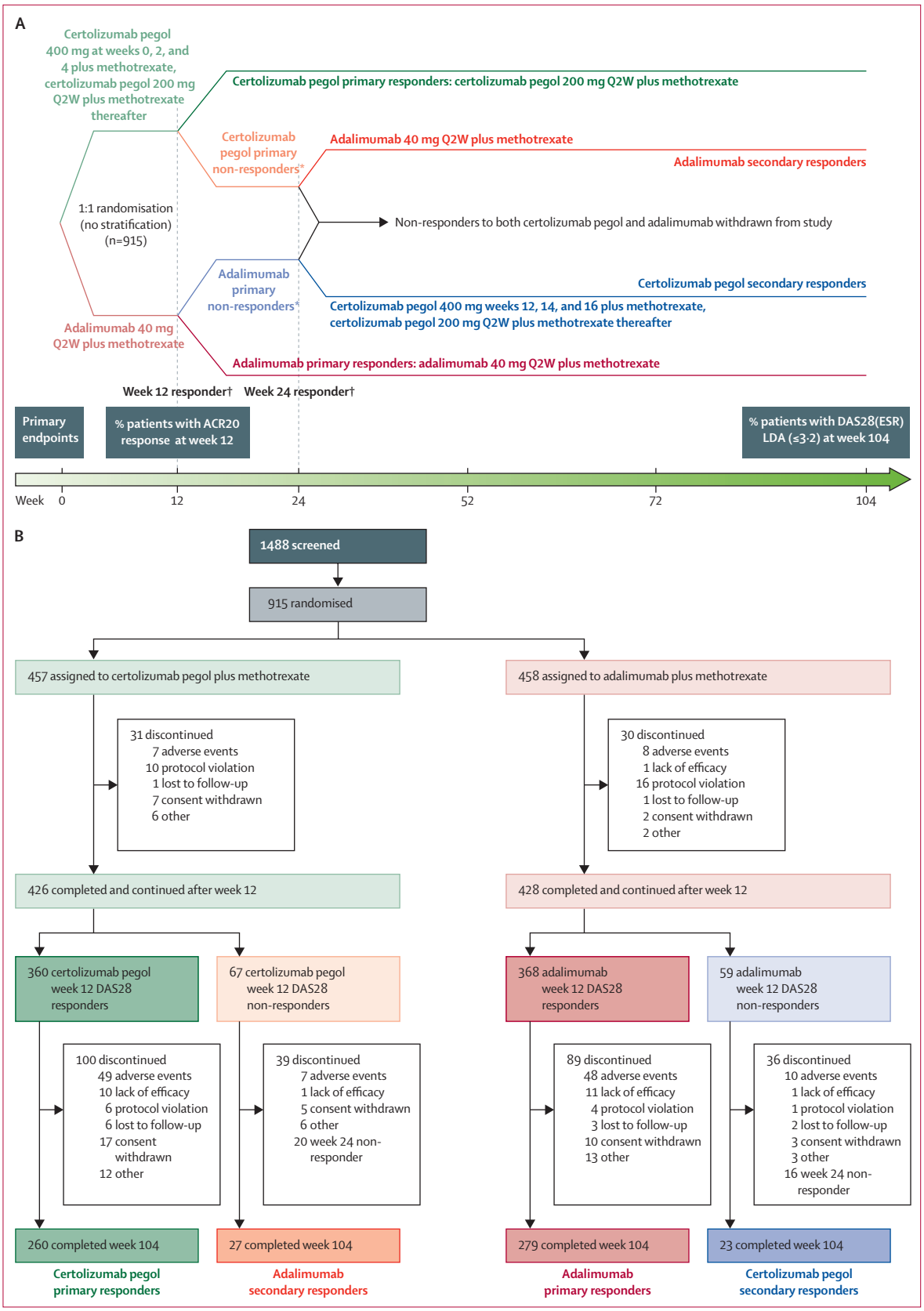

Figure 1: **Study diagram (A) and trial profile (B)**
Week 0–12: double-blind, week 12–104: single-blind; after week 12, there were four subpopulations of patients in EXXELERATE: (1) Primary responders (dark red and dark green lines; n=714); (2) Primary non-responders (light orange and light blue lines; n=122); (3) secondary adalimumab responders (certolizumab pegol to adalimumab switch; light orange line; n=40), and secondary certolizumab pegol responders (adalimumab to certolizumab pegol switch; light blue line; n=33); (4) non-responders to both certolizumab pegol and adalimumab (black line; n=35); the patient numbers provided above are for the full analysis set; Q2W=once every 2 weeks. *DAS28-ESR LDA (≤3·2) or reduction from baseline of ≥1·2. †Week 12 non-responders did not have DAS28-ESR LDA or reduction from baseline (week 12 responder) or week 12 (week 24 responder) of ≥1·2; at week 104, patients who had withdrawn or switched treatments at week 12 were recorded as not being in LDA.

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dose could be reduced to 10 mg after week 12), maintaining the same route of administration (oral or subcutaneous; unless a change in administration route was necessitated due to drug shortage, injection site reaction [for subcutaneous methotrexate], or inability to swallow [for oral methotrexate]), through week 104. Two dose adjustments of methotrexate were permitted at the discretion of the treating rheumatologist; one between week 12 and week 52, and one between week 52 and week 104.

Outcomes

Primary endpoints assessed short-term (week 12) and long-term (week 104) superiority of certolizumab pegol plus methotrexate compared with adalimumab plus methotrexate. The week 12 efficacy endpoint compared the percentage of patients achieving a response of a 20% improvement according to the American College of Rheumatology criteria (ACR20). The week 104 efficacy endpoint compared the percentage of patients achieving LDA (DAS28-ESR ≤3·2); week 12 non-responders were considered LDA non-responders at week 104, even if they achieved LDA after switching to the other TNF inhibitor.

Secondary endpoints compared the percentage of patients with LDA (DAS28-ESR ≤3·2) at weeks 6, 12, and 52, and the change from baseline in health assessment questionnaire-disability index (HAQ-DI) at week 104. Additional secondary endpoints compared the percentage of patients achieving LDA at week 104 for those who had achieved a ACR20 response at week 12, and at both week 6 and week 12. The time to study discontinuation (defined as the number of days from response at week 12 until completion at week 104 or withdrawal before week 104) was also compared between groups.

Other exploratory endpoints included ACR20, ACR50, and ACR70 responses at each study visit, the percentage of patients with sustained remission and LDA (at both week 36 and week 52),[18] maintained remission and LDA (mean LDA/REM for weeks 52, 64, 76, 88, and 100, and LDA/REM at week 104). The percentage of patients with LDA and remission at each study visit was analysed as DAS28-ESR ≤3·2 and <2·6, CDAI ≤10 and ≤2·8 or SDAI ≤11 and ≤3·3, respectively.

Safety analysis included all adverse events and serious adverse events for certolizumab pegol and adalimumab, reported as an exposure-adjusted incidence rate per 100 patient-years. Adverse events and serious adverse events were reported for patients following treatment switch.

Statistical analysis

Sample size was calculated assuming that ACR20 at week 12 would be achieved by 62% of participants in the certolizumab pegol plus methotrexate group and 50% of participants in the adalimumab plus methotrexate group. For DAS28-ESR LDA at week 104 it was assumed that LDA would be achieved by 37·5% of patients in the certolizumab pegol plus methotrexate group and 26·3% of patients in the adalimumab plus methotrexate group, both based on previously reported studies of both medications.[19–21] Using these assumptions, a sample size of 446 patients in the certolizumab pegol plus methotrexate group and 446 patients in the adalimumab plus methotrexate group would provide 90% power to detect a significant difference between treatment groups for each primary endpoint. A two-group continuity-corrected χ^2 test with a two-sided significance level of 0·025 was used.

The full analysis set, which included patients with both baseline and post-baseline DAS28-ESR measurements

	Certolizumab pegol plus methotrexate (safety set, n=457) (full analysis set, n=454)	Adalimumab plus methotrexate (safety set, n=457) (full analysis set, n=454)
Demographics and baseline characteristics		
Age (years)*	53·5 (12·3)	52·9 (12·8)
Sex		
Female*	360 (79%)	362 (79%)
Male	97 (21%)	95 (21%)
BMI (kg/m²)*†	28·5 (6·3)	28·0 (6·3)
Rheumatoid factor		
>14 IU/mL	425 (94%)	422 (93%)
>42 IU/mL	304 (67%)	303 (67%)
Anti-cyclic citrullinated peptide >10 U/mL	368 (81%)	390 (86%)
28-tender joint count	14·8 (6·5)	15·2 (6·5)
28-swollen joint count	10·9 (4·9)	11·2 (5·1)
Erythrocyte sedimentation rate (mm/h)	46·2 (20·7)	45·3 (19·9)
C-reactive protein (mg/L)		
Median (min–max)‡	7·1 (0·2–140·6)	7·9 (0·3–215·7)
Mean (SD)	15·8 (21·8)	15·4 (21·0)
DAS28-ESR	6·5 (0·9)	6·5 (0·9)
DAS28-ESR HDA (>5·1)	431 (95%)	435 (96%)
DAS28-ESR MDA (>3·2 and ≤5·1)	23 (5%)	19 (4%)
HAQ-DI	1·5 (0·6)	1·5 (0·6)
CDAI	38·1 (11·7)	39·2 (11·7)
SDAI	39·8 (12·2)	40·8 (12·1)
Pain (PtAAP, VAS)	62·1 (20·4)	64·6 (20·4)
Patient Global (PtGADA, VAS)	62·0 (20·5)	64·2 (20·1)
Physician Global (PhGADA, VAS)	63·1 (16·1)	64·0 (16·7)
Summary of rheumatoid arthritis history at baseline (safety set)		
Duration of rheumatoid arthritis (years)	6·0 (6·9)	5·8 (6·9)
Median duration of rheumatoid arthritis (years)	3·6	3·1
<1 year	107 (23%)	104 (23%)
1–<2 years	63 (14%)	76 (17%)
2–<5 years	99 (22%)	96 (21%)
5–<10 years	97 (21%)	90 (20%)
≥10 years	91 (20%)	91 (20%)
Presence of extra-articular features§		
History	50 (11%)	51 (11%)
Current	45 (10%)	50 (11%)

(Table 1 continues on next page)

	Certolizumab pegol plus methotrexate (safety set, n=457) (full analysis set, n=454)	Adalimumab plus methotrexate (safety set, n=457) (full analysis set, n=454)
(Continued from previous page)		
Previous TNF inhibitor use (protocol violators)¶	2 (<1%)	2 (<1%)
Methotrexate dose (mg per week)	17·5 (3·8)	18·0 (3·9)
Methotrexate route‖		
Subcutaneous	91 (20%)	81 (18%)
Oral	356 (78%)	371 (82%)
Subcutaneous to oral	2 (<1%)	0
Oral to subcutaneous	3 (1%)	1 (<1%)
Unknown	2 (<1%)	1 (<1%)
Previous corticosteroid use (at baseline)¶	244 (53%)	259 (57%)
Number of previous csDMARDs (excluding methotrexate)		
0 (methotrexate only)	255 (56%)	248 (54%)
1	121 (27%)	135 (30%)
2	52 (11%)	51 (11%)
3	23 (5%)	19 (4%)
4	3 (1%)	2 (<1%)
>4	3 (1%)	2 (<1%)

Data are mean (SD) or n (%). All data are for full analysis set unless otherwise stated. HDA=high disease activity. MDA=medium disease activity. HAQ-DI=Health Assessment Questionnaire Disability Index. CDAI=Clinical Disease Activity Index. SDAI=Simplified Disease Activity Index. PhGADA=physician's global assessment of disease activity. PtAAP=patient's assessment of arthritis pain. PtGADA=patient's global assessment of disease activity. VAS=visual analogue scale (0–100 mm). *Safety set. †For body-mass index, n=455 for certolizumab pegol plus methotrexate group and n=454 for adalimumab plus methotrexate group. ‡High-sensitivity CRP upper limit of normal (ULN) was 3 mg/L. §Extra-articular manifestations included keratoconjunctivitis sicca, rheumatoid nodules, scleritis, neuropathy, vasculitis, and pulmonary fibrosis. ¶Previous medications are defined as those that were initiated before the first dose of the study drug.

Table 1: **Demographics, baseline characteristics, and rheumatoid arthritis history at baseline**

(three patients in the certolizumab pegol plus methotrexate group and four patients in the adalimumab plus methotrexate group did not meet these criteria and were excluded from the full analysis set), and the week 12 full analysis set (patients in the randomised set who received at least one dose of study drug after week 12 and had valid baseline, week 12 and post-week 12 efficacy measurements) were used for all efficacy analyses. An analysis of the per-protocol set (ie, all patients without important protocol deviations that could influence the validity of the primary endpoint) was prespecified in the statistical analysis plan on the condition that >15% of patients in the full analysis set were excluded from the per-protocol set; however, this analysis was not done because less than 15% of the patients met the criteria for exclusion from the per-protocol set. The safety set (patients who received at least one dose of study drug) and the week 12 safety set (all patients in the safety set who received at least one dose of study drug after the week 12 visit) were used for all safety analyses. Safety data are presented according to the treatment actually received.

Time to study discontinuation, defined as the number of days from week 12 until completion at week 104 or until withdrawal before week 104, was calculated using Kaplan-Meier methods. Week 12 responders who completed the study were censored at the final documented study visit. Between group differences were analyzed using the log-rank statistic

Data were analysed with SAS version 9.2. Treatment differences for selected adverse event categories were assessed using nominal p values based on Fisher's exact test for categorical variables and the two sample *t* test for continuous variables. For the analysis of the primary endpoints, the Hochberg method was prespecified to account for multiplicity.[22] ACR20 and DAS28-ESR LDA primary and secondary analyses were carried out using a logistic regression model, including terms for gender, age, disease duration, and geographic region. For DAS28-ESR LDA, baseline DAS28-ESR value was also included as a covariate. Change from baseline in HAQ-DI at week 104 was examined by comparing the randomised treatment groups using an analysis of covariance model with the following terms: baseline score, gender, age, disease duration, and geographic region. Non-responder imputation (NRI) was used to impute missing values for dichotomous efficacy variables and last observation carried forward for continuous efficacy variables. For primary and secondary endpoints based on the full analysis set that were evaluated after week 12, non-responders at week 12 were imputed as non-responders at the given subsequent visit for dichotomous variables, while the week 12 value was carried forward to the relevant visit for continuous variables.

Role of the funding source

CC, CE, LG, LI, and LP are company employees of UCB Pharma and contributed to the study design, data analysis, data interpretation, and writing of the report, but had no involvement in data collection. The authors had full access to all of the study data and had final responsibility for the decision to submit for publication. All monitoring was done by Parexel (an external contract research organisation) and 100% of the study was source verified. The study was funded by UCB Pharma.

Results

Between Dec 14, 2011, and Nov 11, 2013, 1488 patients were screened, of whom 915 were randomly assigned; 457 to certolizumab pegol plus methotrexate and 458 to adalimumab plus methotrexate. Of these, 457 participants assigned to certolizumab pegol plus methotrexate were included in the safety set and 457 participants assigned to adalimumab plus methotrexate were included in the safety set. 454 participants assigned to certolizumab pegol plus methotrexate and 454 assigned to adalimumab plus methotrexate were included in the full analysis set. 426 assigned to certolizumab pegol plus methotrexate and 427 assigned to adalimumab plus methotrexate were included in the week 12 safety set. 418 assigned to certolizumab pegol plus methotrexate and 418 assigned to adalimumab plus methotrexate were included in the week 12 full analysis set (figure 1B). Baseline characteristics and levels of disease activity were generally similar between treatment groups (table 1).

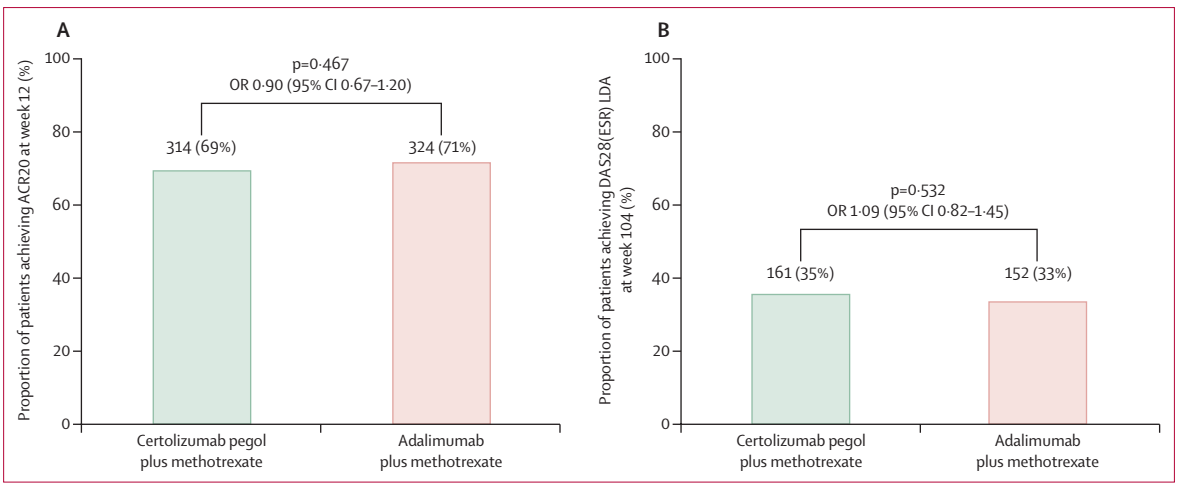

Figure 2: **Primary endpoints**
(A) Percentage of patients achieving ACR20 at week 12 and (B) percentage of patients achieving DAS28-ESR LDA at week 104 (full analysis set, non-responder imputation). OR=odds ratio. LDA is defined as DAS28-ESR ≤3·2. Patients not achieving DAS28-ESR reduction ≥1·2 or DAS28-ESR ≤3·2 at weeks 12 were classed as non-responders at week 104. DAS28-ESR=Disease Activity Score 28-erythrocyte sedimentation rate. LDA=rate low disease activity.

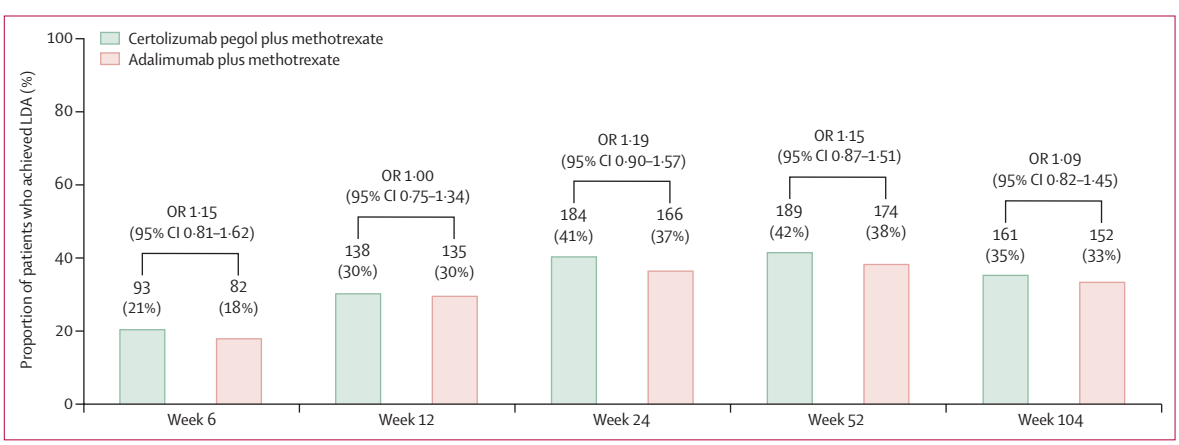

Figure 3: **DAS28-ESR LDA at weeks 6, 12, 24, 52, and 104 (full analysis set, non-responder imputation)**
Patients not achieving DAS28-ESR reduction ≥1·2 or DAS28-ESR ≤3·2 at weeks 12 were classed as non-responders at week 104. LDA is defined as DAS28-ESR ≤3.2. OR=odds ratio. DAS28-ESR=Disease Activity Score 28-erythrocyte sedimentation rate. LDA=low disease activity.

The most common reasons for study discontinuation between baseline and week 12 in the randomised set were adverse events (seven [2%] of 457 in the certolizumab pegol plus methotrexate group and eight [2%] of 458 in the adalimumab plus methotrexate group) and protocol violation (ten [2%] in the certolizumab pegol plus methotrexate group and 16 [4%] in the adalimumab plus methotrexate group). Between week 12 and week 104, the most common reason for study discontinuation in primary responders were adverse events (49 [14%] of 360 in the certolizumab pegol plus methotrexate group and 48 [13%] of 368 in the adalimumab plus methotrexate group. 67 (15%) of 457 participants in the certolizumab pegol plus methotrexate group and 59 (13%) of 458 participants in the adalimumab plus methotrexate group did not meet the response criteria to their initial therapy and were classified as primary non-responders; of those, 65 participants in the certolizumab pegol plus methotrexate group who were primary non-responders were switched to adalimumab plus methotrexate and 57 participants in the adalimumab plus methotrexate group who were primary non-responders were switched to certolizumab pegol plus methotrexate and were included in the week 12 full analysis set. The most common reasons for study discontinuation between week 12 and week 104 for primary non-responders were adverse events (seven [11%] of 66 participants who switched to adalimumab plus methotrexate and ten [17%] of 59 who switched to certolizumab pegol plus methotrexate) and protocol-mandated withdrawal of week 24 non-responders (20 [30%] of 66 participants who switched to adalimumab plus methotrexate and 16 [27%] of 59 participants who switched to certolizumab pegol plus methotrexate; figure 1B).

The results of the primary analysis did not show superiority of certolizumab pegol plus methotrexate over adalimumab plus methotrexate, with no significant

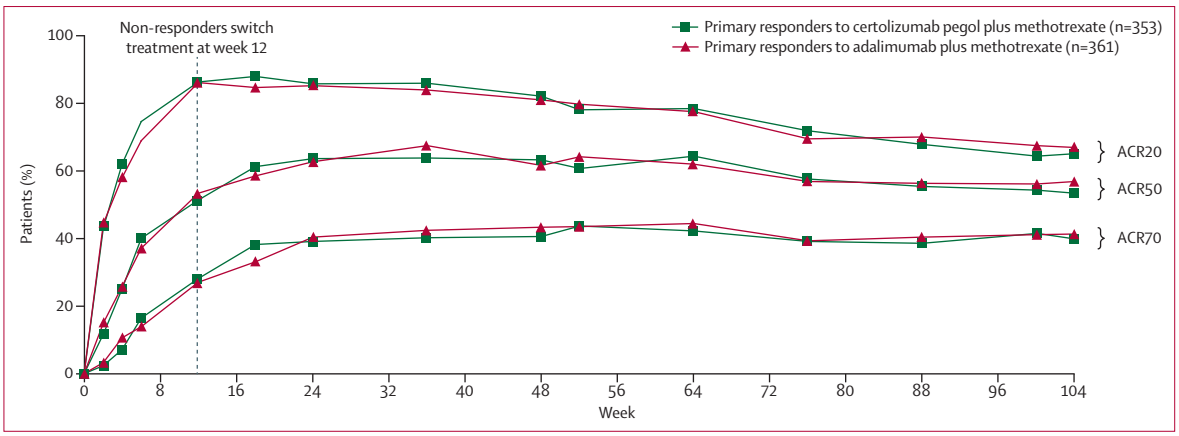

Figure 4: **Percentage of patients achieving ACR20, ACR50, and ACR70 response at each study visit (week 12 full analysis set, non-responder imputation)**
ACR=American College of Rheumatology.

difference in week 12 ACR20 response (314 [69%] and 324 [71%]; odds ratio [OR] 0·90 [95% CI 0·67–1·20], p=0·467) or week 104 DAS28(ESR) LDA (161 [35%] and 152 [33%]; OR 1·09 [95% CI: 0·82, 1·45], p=0·532) between certolizumab pegol plus methotrexate and adalimumab plus methotrexate, respectively (figure 2; assessed by logistic regression).

The secondary efficacy endpoints were similar between certolizumab pegol plus methotrexate and adalimumab plus methotrexate patients in the full analysis set (figure 3). Physical functioning improved for both treatment groups. Change from baseline in HAQ-DI at week 104 was –0·62 for patients assigned to certolizumab pegol plus methotrexate and –0·72 for patients assigned to adalimumab plus methotrexate (appendix p 2), and post-hoc analysis shows that normative physical function (HAQ-DI ≤0·25[23]) was achieved by 92 (20%) of 454 patients assigned to certolizumab pegol plus methotrexate and 101 (22%) of 454 patients assigned to adalimumab plus methotrexate.

See Online for appendix

For primary responders, the results for exploratory efficacy variables were similar for both groups. ACR20 responses at week 104 were achieved by 229 (65%) of 353 certolizumab pegol and 241 (67%) of 361 adalimumab primary responders, ACR50 responses at week 104 were achieved by 188 (53%) of 353 certolizumab pegol and 205 (57%) of 361 adalimumab primary responders, and ACR70 responses at week 104 were achieved by 140 (40%) of 353 certolizumab pegol and 149 (41%) of 361 adalimumab primary responders (figure 4; appendix p 6).

For the primary non-responder patient population, clinical disease activity did not improve between baseline and week 12; some variables deteriorated (appendix p 7). Overall, for these primary non-responders, 33 (56%) of 57 switching to certolizumab pegol and 40 (62%) of 65 switching to adalimumab became responders 12 weeks later (week 24) by achieving DAS28-ESR of 3·2 or less or a DAS28-ESR reduction from week 12 of 1·2 or higher; these patients were classified as secondary responders (appendix p 6). Patients not responding by week 24 (ie, 12 weeks after switching, and thus double non-responders) were withdrawn. The baseline demographics of this double non-responder patient population and the baseline demographics of the primary responders are given in the appendix (p 8). On average, among primary non-responders, following treatment switch from one TNF inhibitor to the alternative TNF inhibitors at week 12, all clinical variables improved substantially over the first 12 weeks following treatment switch (ie, at week 24 from study baseline, and compared with week 12). For certolizumab pegol primary non-responders switching to adalimumab, ACR20 response rate was 40% (26/65), ACR50 response rate was 17% (11/65), and ACR70 response rate was 8% (five of 65); in this population, DAS28-ESR LDA was 19% (12/65), and CDAI LDA was 26% (17/65).

Comparable results were observed at week 12 following treatment switch to certolizumab pegol; ACR20 response rate was 44% (25/57), ACR50 response rate was 23% (13/57), and ACR70 response rate was 11% (6/57), DAS28-ESR LDA was 21% (12/57), and CDAI LDA was 33% (19/57) in this population. At week 36 (ie, 24 weeks post-switch, which has been the usual endpoint in previous trials[24–26] of TNF inhibitor-inadequate responder patients), ACR20 responses were achieved by 35% (23/65), ACR50 by 20% (13/65), and ACR70 by 11% (7/65) of certolizumab pegol patients switching to adalimumab, and ACR20 responses were achieved by 30% (17/57), ACR50 by 19% (11/57), and ACR70 by 11% (6/57) of adalimumab patients switching to certolizumab pegol. The time courses of various outcomes in primary non-responders who switched treatment, secondary responders, and double non-responders are shown in figure 5.

Additional secondary endpoints in the respective patient populations are shown in the appendix (pp 2–5, pp 6–8); similar results were noted between treatment groups in these parameters.

For patients receiving study drug at any time during the trial, the incidence per 100 patient-years of treatment-emergent adverse events (certolizumab pegol 139·9 and adalimumab 134·8), serious treatment-emergent adverse

events (9·4 and 7·7), or serious infections and infestations (2·2 and 2·0) by treatment at adverse event onset (treatment-emergent adverse event rate per 100 patient-years 257·5 *vs* 260·0, respectively; table 2) were similar for certolizumab pegol and adalimumab, respectively.

The number of patients reporting serious treatment-emergent adverse events by treatment at any time over the 2 years of the study was similar for certolizumab pegol plus methotrexate (67 [13%] of 516) and adalimumab plus methotrexate (58 [11%] of 523). Malignancies occurred in 15 patients (defined by treatment at adverse event onset): eight patients in the certolizumab pegol group and seven patients in the adalimumab group (basal cell carcinomas in three certolizumab pegol and two adalimumab patients; one bladder cancer and one invasive ductal breast carcinoma in both adalimumab and certolizumab pegol arms; squamous cell carcinoma, fatal lung adenocarcinoma, and thyroid cancer was reported in the certolizumab pegol arm only; B-cell lymphoma, chronic myeloid leukaemia, and renal cancer in the adalimumab group only).

The incidence rate of infections and infestations was 59·9 for certolizumab pegol plus methotrexate and 59·1 for adalimumab plus methotrexate; the number of serious infections was similar between groups (table 2). There was a single case of disseminated tuberculosis during the study in a patient treated with adalimumab plus methotrexate, and six opportunistic infections: three mycobacterium infections in the certolizumab pegol group, and two candidiasis and one aspergillosis in the adalimumab group.

Three deaths were reported in each group. In the certolizumab pegol group, two deaths were caused by cardiovascular events (coronary artery disease and myocardial infarction) and one by respiratory non-small cell malignancy. In the adalimumab group, one was a sudden death, one death caused by pneumonia, and one by bronchopulmonary aspergillosis.

The percentage of primary non-responders reporting treatment emergent adverse events following treatment switch and within 70 days following the final dose of initial study drug (about 5·5 drug half-lives) was similar for each group (24 [41%] of 59 patients who received certolizumab pegol plus methotrexate and 30 [46%] of 66 patients who received adalimumab plus methotrexate; appendix p 9). This similarity between treatment groups was also seen after 70 days of the final dose of the initial study drug (28 [53%] of 53 patients (due to drop out) who received certolizumab pegol plus methotrexate and

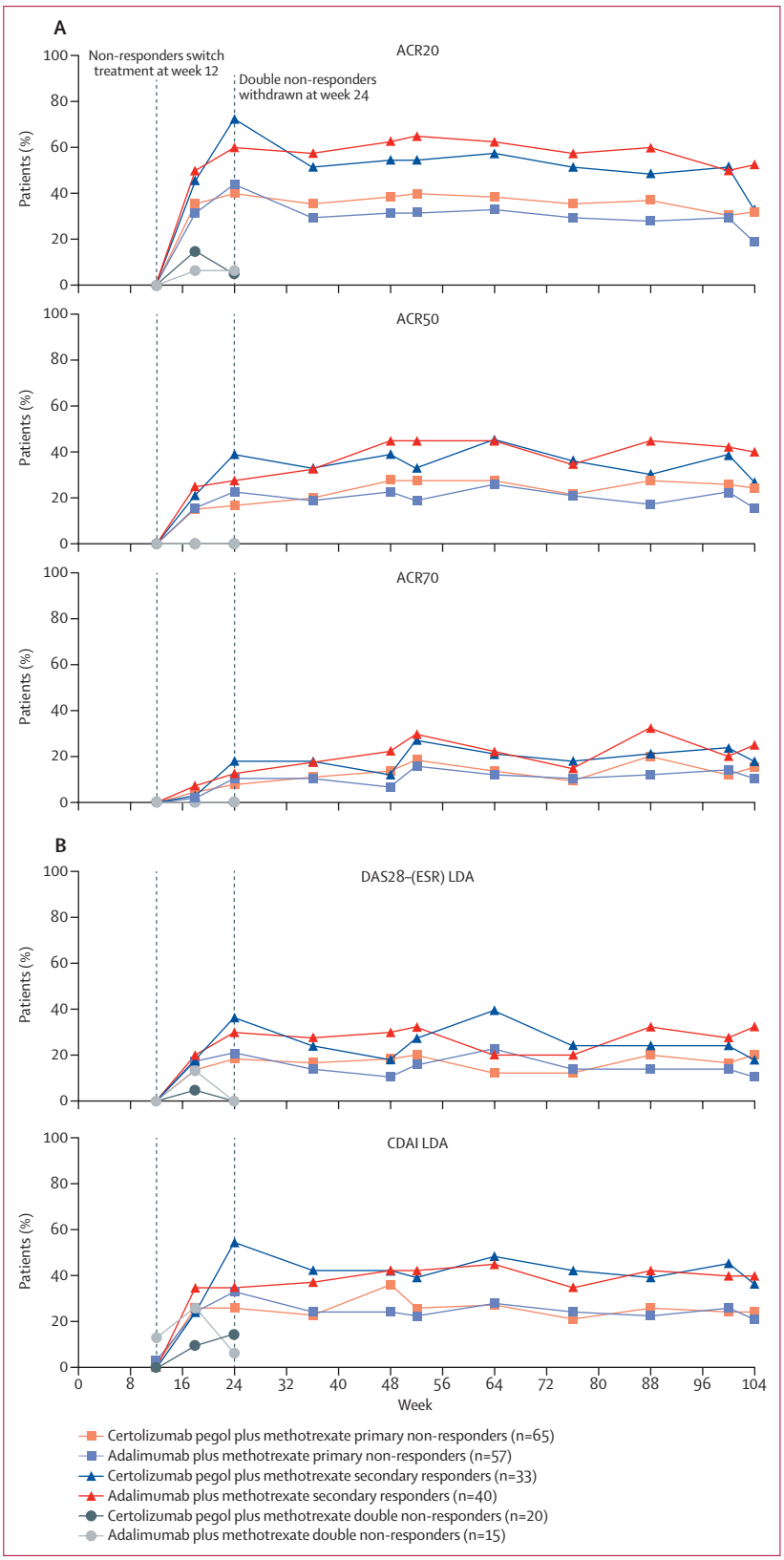

Figure 5: **Exploratory endpoints, primary non-responders, secondary responders, and double non-responders**
(A) Percentage of patients achieving ACR20, ACR50, and ACR70 response at each study visit (week 12 full analysis set, non-responder imputation). (B) Percentage of patients achieving DAS28-ESR and CDAI LDA at each study visit (week 12 full analysis set, non-responder imputation). Patients not achieving DAS28-ESR reduction ≥1·2 or DAS28-ESR ≤3·2 at weeks 12 were classed as non-responders at week 104. ACR=American College of Rheumatology. DAS28-ESR=Disease Activity Score 28-erythrocyte sedimentation rate. LDA=low disease activity. CDAI=clinical disease activity index

	Certolizumab pegol plus methotrexate (n=516)		Adalimumab plus methotrexate (n=523)		Nominal p value for treatment difference
	n (%)	Incidence (95% CI)	n (%)	Incidence (95% CI)	
Any treatment-emergent adverse events	389 (75%)	139·9 (126·4–154·5)	386 (74%)	134·8 (121·7–149·0)	0·569
Serious treatment-emergent adverse events	67 (13%)	9·4 (7·3–11·9)	58 (11%)	7·7 (5·9–10·0)	0·391
Serious infections and infestations	17 (3%)	2·2 (1·3–3·6)	16 (3%)	2·0 (1·2–3·3)	0·861
Serious cardiac disorders	8 (2%)	1·1 (0·5–2·1)	9 (2%)	1·1 (0·5–2·2)	>0·999
Serious vascular disorders	4 (1%)	0·5 (0·1–1·3)	0	0·0	0·061
Discontinuation due to treatment-emergent adverse events	65 (13%)	8·7 (6·7–11·0)	63 (12%)	8·1 (6·2–10·3)	0·850
All malignancies	8 (2%)	1·1 (0·5–2·1)	7 (1%)	0·9 (0·4–1·8)	0·801
All malignancies (excluding NMSC)	5 (2%)	0·7 (0·2–1·5)	5 (1%)	0·6 (0·2–1·5)	>0·999
Opportunistic infections (excluding tuberculosis)	3 (1%)	0·4 (0·1–1·1)	3 (1%)	0·4 (0·1–1·1)	>0·999
Tuberculosis (confirmed)	0	0·0	1 (<1%)	0·1 (0·0–0·7)	>0·999
Deaths (treatment-emergent adverse events leading to death)	3 (1%)	..	3 (1%)	..	>0·999

Nominal p values are based on Fisher's exact test. Mean time of drug exposure was 545·6 days for certolizumab pegol plus methotrexate and 552·6 days for adalimumab plus methotrexate. Safety set percentages are based on the actual treatment received among patients who took study drug at any time. Patients who received certolizumab pegol plus methotrexate and adalimumab plus methotrexate are counted after respective switching in both columns. Treatment-emergent adverse events were defined according to MedDRA version 18.1. NMSC=non-melanoma skin cancer.

Table 2: **Overview of incidence of treatment-emergent adverse events by treatment at adverse event onset by system organ class**

35 [59%] of 59 patients who received adalimumab plus methotrexate; table 3). After switch, and within 70 days of the last dose of initial study drug, no serious infection events were reported in either switcher population.

Discussion

The EXXELERATE study is the first prospective, single blind (double blind to week 12 and investigator blind thereafter) trial, assessing the efficacy of one TNF inhibitor, certolizumab pegol, compared with another, adalimumab, with a primary superiority endpoint at 12 weeks and 2 years, among patients with rheumatoid arthritis receiving background methotrexate. In this study, despite differences in approved dosing (such as a loading dose for certolizumab pegol), the results in the predefined analyses showed no superiority of certolizumab pegol in the short-term and long-term endpoints. The results also provide direct head-to-head clinical evidence that the safety profile over 2 years is comparable, including serious and opportunistic infections. Importantly, in this study, patients with an inadequate response to the first TNF inhibitor at 12 weeks were switched to the other TNF inhibitor; these patients had all not responded to only one other type of TNF inhibitor and, therefore, are a homogeneous, primary non-responder population.

All previous studies of populations with inadequate responses to TNF inhibitors have included patients who were retrospectively defined as such by physician assessment and not by clear, prospective evidence of a primary inadequate response to a TNF inhibitor. Moreover, several clinical trials assessing the efficacy and safety of bDMARDS with different mechanisms of action in rheumatoid arthritis have enrolled patients who have not responded adequately to treatment with one or more previous bDMARDs and included both primary and secondary non-responders. These studies include the ATTAIN,[23] REFLEX,[24] and RADIATE[25] trials. ACR20 response rates reported in these trials were in the range of 50%, ACR50 of 25%, and ACR70 of 10%, which are higher than we observed in our primary non-responder switcher population for ACR20, but quite similar for ACR50 and ACR70 responses. Previously, it was postulated that patients who are primary non-responders, as in EXXELERATE, are very unlikely to respond to treatment with a second TNF inhibitor and that these patients should switch to treatment with a drug with another mechanism of action.[27,28] Although there are significant differences in study design and patient populations between this trial and others testing efficacy of bDMARDs in patients who had previously had an inadequate response to TNF inhibitors,[24–26] the ACR20, ACR50 and ACR70 response rates clearly show that some patients will benefit by immediately switching from one TNF inhibitor to another if they have an insufficient response to their primary TNF inhibitor at week 12. Although ACR guidelines recommend switching non-responding patients to treatments that use a different mechanism of action, the approach described here (ie, switching non-responding patients to a second TNF inhibitor) is an option in current EULAR recommendations for the management of rheumatoid arthritis[3,4] and is now further supported by the findings of this study. However, it is currently unclear why patients who fail one TNF inhibitor respond to another one, and this question is an important focus for future research.

The non-responder population that switched at week 12 showed no clinical improvement from baseline and

showed worsening in some factors—eg, DAS28-ESR, CDAI and SDAI. However, some of these patients responded to treatment with a second TNF inhibitor. Since attaining low disease activity is a desirable treatment target, it is particularly noteworthy that the proportion of patients who achieved LDA 12 weeks after switching treatment (19% of certolizumab pegol patients switching to adalimumab, 21% of adalimumab patients switching to certolizumab pegol) is quite considerable for this refractory population.

Before this study, the body of evidence supporting the use of TNF inhibitors after initial TNF inhibitor failure was limited, because no trials have assessed the efficacy of an immediate switch from one TNF inhibitor to another.[3] The results from EXXELERATE suggest that different TNF inhibitors might have efficacy in one patient but not in another, potentially due to differences in patient subtypes or due to differences between certolizumab pegol and adalimumab, and, therefore, support the use of a second TNF inhibitor in primary TNF inhibitor non-responsive patients, an observation which might be used to support further updates to both the EULAR recommendations and ACR guidelines. Furthermore, when initiating treatment with either certolizumab pegol or adalimumab and following the treatment strategy described in this study (ie, switching non-responders to the alternative treatment at week 12), LDA was achieved by 44% of patients at week 36 (24 weeks post switch), including both the primary and secondary responders, which is a valuable result for patients in this population, many of whom had had unsuccessful treatment with multiple csDMARDs.

In clinical practice, there are differences in the approaches taken to treatment switch, both with regards to the drug washout period before the start of a new drug and in the use of a loading dose of certolizumab pegol. These inconsistencies are potentially driven by safety concerns about concomitant exposure to two different TNF inhibitors, despite a lack of any supporting evidence. In previous trials,[14,15,24–26] TNF inhibitor inadequate-responder patients had their TNF inhibitor discontinued several weeks to months before entry into the trial, and so the effects of a direct switch in terms of efficacy and safety were unknown. This study provides reassuring evidence, albeit in a relatively small group of patients, that supports the safety of an immediate switch between certolizumab pegol and adalimumab without a washout period, as shown by the absence of any serious infections occurring within the 70 day period post-switch.

This study had several limitations. It was limited to two particular TNF inhibitors, and extrapolating these results to other TNF inhibitors might not be appropriate. In addition, patients were not blind to treatment after week 12 of the study. Consequently, patient-reported outcomes could have been biased,[29] although the primary components of ACR20/50/70 response are the joint count reductions, which were assessed by the blinded investigator. This expectation bias could have been further inflated because all participants and physicians knew the drugs were active (ie, there was no placebo). Assumptions used to calculate the study sample size were based on analyses of findings from several studies,[19–21] which supported a superiority hypothesis of certolizumab pegol over adalimumab. A non-inferiority design, using the same assumptions, could have been used to define a primary endpoint. Using a non-inferiority margin of 12% (as per previous non-inferiority trials—eg, AMPLE[5]) would have resulted in formal demonstration of non-inferiority, because the confidence intervals for the difference in proportions for the two primary endpoints (ACR20, –8·5 to 3·9; DAS28-ESR LDA, –4·2 to 8·1) would have been within a 12% non-inferiority margin. However, because a non-inferiority analysis and corresponding margin were not prespecified, a conclusion related to non-inferiority cannot be made.

In conclusion, this study showed no significant difference in efficacy between certolizumab pegol and adalimumab in the treatment of rheumatoid arthritis, with similar safety data, over either the short term (12 weeks) or long term (2 years). These data also emphasise the value of the use of a second TNF inhibitor in patients who have not responded to 12 weeks of treatment with a first TNF inhibitor, lending further support to the treat-to-target principle in rheumatoid arthritis patients. The EXXELERATE study indicates that both certolizumab pegol and adalimumab have comparable safety profiles over a 2-year period, and provides reassuring evidence of the safety of switching between certolizumab pegol and adalimumab without a washout period. In view of the similarities of efficacy and safety of these two TNF inhibitors, treatment costs might become a more important factor in clinical decision making,[4,30] especially considering inequalities surrounding access to treatment.[31–33] Furthermore, in an increasingly cost-driven environment, EXXELERATE reiterates the value of switching from one bDMARD to a second, here specifically for TNF inhibitors, when the first drug fails to convey an adequate response within a predetermined time interval as suggested by the treat to target approach, endorsed by both ACR and EULAR.[3,4] As such, the ability to make a treatment decision at 3 months, as shown in this trial, should minimise resource allocation to an ineffective therapy.

Contributors

All authors were involved in the EXXELERATE study, reviewed and interpreted the data, developed the manuscript, and approved the final draft. BC, SH, JRC, and RF also enrolled patients into the study.

Declaration of interests

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