RHEUMATOLOGY

Rheumatology 2012;51:2204–2214
doi:10.1093/rheumatology/kes150
Advance Access publication 25 August 2012

Original article

Efficacy and safety of certolizumab pegol in a broad population of patients with active rheumatoid arthritis: results from the REALISTIC phase IIIb study

Michael E. Weinblatt[1], Roy Fleischmann[2], Tom W. J. Huizinga[3], Paul Emery[4], Janet Pope[5], Elena M. Massarotti[1], Ronald F. van Vollenhoven[6], Jürgen Wollenhaupt[7], Clifton O. Bingham III[8], Ben Duncan[9], Niti Goel[10], Owen R. Davies[11] and Maxime Dougados[12]

Abstract

Objective. To investigate the efficacy and safety of certolizumab pegol (CZP) in a broad population of patients with active RA.

Methods. In this 12-week, double-blind period of the phase IIIb trial, RA patients with inadequate response to at least one DMARD were randomized 4:1 to CZP (400 mg at weeks 0, 2 and 4, followed by 200 mg every 2 weeks) or placebo (every 2 weeks) plus current therapy stratified by previous TNF inhibitor use, concomitant methotrexate use and disease duration (<2 *vs* $\geqslant 2$ years). The primary outcome was ACR20 response rate at week 12.

Results. Of 1063 patients (CZP = 851; placebo = 212), 37.6% had previous TNF inhibitor use. Baseline mean HAQ Disability Index (HAQ-DI) and DAS 28-joint assessment-ESR [DAS28(ESR)] values were 1.5 and 6.4 in the CZP group, and 1.6 and 6.4 in the placebo group, respectively. The primary endpoint was significant (week 12 ACR20, CZP *vs* placebo: 51.1 *vs* 25.9%; $P < 0.001$); differences were noted at week 2 (31.8 *vs* 8.5%; $P < 0.001$). HAQ-DI and DAS28(ESR) change from baseline and ACR50 were significant from week 2. Week 12 ACR20 responses were similar across CZP patient subgroups regardless of concomitant DMARD use at baseline. Adverse and serious adverse events were comparable between CZP and placebo, with no new safety signals.

Conclusion. CZP was associated with rapid and consistent clinical responses and improved physical function in a diverse group of RA patients, irrespective of concomitant or previous therapy.

Trial registration. ClinicalTrials.gov, http://clinicaltrials.gov/, NCT00717236.

Key words: rheumatoid arthritis, biologicals, tumour necrosis factor.

CLINICAL SCIENCE

[1]Division of Rheumatology, Immunology and Allergy, Brigham and Women's Hospital, Boston, MA, [2]MCRC, University of Texas, Dallas, TX, USA, [3]Leiden University Medical Centre, Leiden, The Netherlands, [4]Section of Musculoskeletal Disease, Leeds Institute of Molecular Medicine, University of Leeds, NIHR Leeds Musculoskeletal Biomedical Research Unit, Leeds Teaching Hospitals NHS Trust, Leeds, UK, [5]St Joseph's Health Care, University of Western Ontario, London, ON, Canada, [6]Karolinska Institute, Stockholm, Sweden, [7]Schoen Klinik Hamburg Eilbek, Hamburg, Germany, [8]Johns Hopkins University, Baltimore, MD, [9]UCB Pharma, Raleigh, NC, USA, [10]UCB Pharma, Smyrna, GA, USA, [11]UCB Pharma, Brussels, Belgium and [12]AP-HP Cochin Hospital, Rene Descartes University, Paris, France.

Submitted 23 December 2011; revised version accepted 23 April 2012.

Correspondence to: Michael E. Weinblatt, Harvard Medical School, Division of Rheumatology, Immunology and Allergy, Brigham and Women's Hospital, 75 Francis Street, Boston, MA 02115, USA.
E-mail: mweinblatt@partners.org

Present address: Niti Goel, General Medicine Therapeutic Delivery Unit, Quintiles, Durham, NC, USA.

Introduction

Clinical trials demonstrate that TNF inhibitors, especially when administered with MTX, improve the signs and symptoms of RA and slow radiographic progression in a majority of patients with active RA [1–4]. However, clinical trial populations comprise a largely homogeneous patient group that may not reflect patients seen in routine clinical care [5, 6].

In general, there is a lack of double-blind randomized studies that have evaluated TNF inhibitor therapy in a diverse group of patients to compare efficacy across subpopulations, such as those with and without previous TNF inhibitor use, with and without baseline MTX use, and with treatment as monotherapy or

with non-MTX DMARDs [2–4], irrespective of disease duration.

The anti-TNF agent certolizumab pegol (CZP) as monotherapy or as an add-on therapy to MTX significantly improved the signs and symptoms of RA compared with placebo or MTX plus placebo in patients with moderate to severe active RA who were TNF inhibitor-naïve and had been treated with non-MTX DMARDs [7–9]. The REALISTIC (RA Evaluation in Subjects Receiving TNF Inhibitor CZP) study investigated the safety and efficacy of CZP as monotherapy or as an addition to current treatment in a broader population of RA patients resembling those seen in clinical settings. In this placebo-controlled 12-week study, CZP was evaluated in patients with active, inadequately controlled RA, irrespective of disease duration and using a broad range of previous and current medications, including anti-TNF agents.

Materials and methods

Patients

Eligible patients were ⩾18 years of age, had adult-onset RA as defined by the 1987 ACR criteria [10] for at least 3 months and showed an unsatisfactory response or intolerance to at least one DMARD (MTX, LEF, SSZ, chloroquine or HCQ, AZA and/or gold). Subjects had active disease as defined by at least five tender and at least four swollen joints (28-joint count) and either ⩾10 mg/l CRP or ⩾28 mm/h ESR (Westergren method) at screening. Exclusion criteria included the following: a history of chronic, serious, or life-threatening infection; any current infection; a history of or currently active tuberculosis (TB); evidence of latent TB defined as a positive purified protein derivative skin test (⩾5 mm) or had close contact with individuals with active TB. Patients positive for purified protein derivative could be included if active TB was ruled out and if they were adequately treated for latent TB [e.g. isonicotinic acid hydrazide for 9 months (with vitamin B6)], with treatment initiated at least 1 month before first administration with the study drug. Etanercept and anakinra should have been discontinued at least 1 month before study entry, and other biologic RA therapies within 2 months of study entry. Patients were excluded who received treatment either with more than two TNF inhibitors, rituximab or abatacept. Analgesics, oral CSs (⩽10 mg/day prednisone equivalent) and NSAIDs/cyclo-oxygenase 2 inhibitors were permitted if doses were stable within 24 h, 7 days and 14 days of baseline, respectively. IA hyaluronic acid within 4 weeks of baseline was prohibited, and patients were excluded if they received the following DMARDS within 3 months of baseline: cyclosporin, CYC, MMF, chlorambucil and penicillamine. Patients were allowed to use DMARDs listed later in the text in the study design at the same stable dosage as at baseline through week 12. IA, i.m. and i.v. CSs were not permitted within 4 weeks of baseline, and no more than one IA CS injection was allowed between baseline and week 8.

Study design

This 12-week, double-blind period of a phase IIIb study with an open-label extension phase (a minimum of 16-weeks open-label treatment and 12 weeks of safety follow-up) was conducted between July 2008 and March 2010 in 230 centres in the USA and Canada (75%) and Europe (25%). The study complied with the principles of the Declaration of Helsinki and was approved by the institutional review boards at each participating centre. All patients provided written informed consent. This study is registered at ClinicalTrials.gov, NCT00717236.

Patients were randomized 4:1 via an interactive voice-response system and stratified by baseline MTX use, previous TNF inhibitor use and disease duration (<2 *vs* ⩾2 years) to receive either CZP 400 mg at weeks 0, 2 and 4, followed by CZP 200 mg every 2 weeks or placebo injection (control; 0.9% sodium chloride) every 2 weeks in addition to their current RA treatment (if any), which could include any combination of the following: DMARDs (MTX, LEF, SSZ, chloroquine or HCQ, AZA and/or gold), tetracyclines, glucocorticoids (prednisone equivalent ⩽10 mg/day) and NSAIDs/cyclo-oxygenase 2 inhibitors. Patients completing the 12-week, double-blind phase were eligible to receive open-label CZP 200 mg every 2 weeks for ⩾16 weeks. Results from the 12-week, double-blind phase are reported here based on the final database at the completion of the trial.

Efficacy and safety evaluations

Efficacy and safety evaluations were performed at baseline and at weeks 2 (first post-baseline assessment), 6 and 12. The primary efficacy end point was the ACR20 response rate at week 12. Pre-specified secondary end points were as follows: ACR50/70 response rates at week 12; reduction of disease activity by DAS 28-joint assessment based on CRP [DAS28(CRP)]; DAS28(CRP) <2.6 (remission); improvement in individual components of the ACR core criteria; ACR20 response rates at week 12 based on stratification by baseline MTX and previous TNF inhibitor use and disease duration (<2 *vs* ⩾2 years).

Post hoc analyses included the following: reduction of disease activity in all patients as assessed by DAS28 (ESR); week 12 ACR50/70 responses rates based on baseline stratification parameters as indicated previously; concomitant DMARDs; use of MTX at baseline with no previous TNF inhibitor use; number (1 or 2) and type of previous TNF inhibitors (adalimumab, etanercept, infliximab); reasons for discontinuation of previous TNF inhibitors (efficacy and non-efficacy reasons), number (0, 1 or ⩾2) and type of concomitant DMARDs (MTX, LEF, SSZ and HCQ) and number of previous DMARDs (1, 2 or ⩾3).

Safety assessments included physical examination, measurement of vital signs and laboratory parameters (performed at a central laboratory, with the exception of ESR) and recording of adverse events (AEs) at each visit. Any important medical event, including events that did not require hospitalization, such as certain opportunistic infections, was considered a serious adverse event (SAE).

All patients were evaluated for signs and symptoms of active TB and assessed for the risk of exposure to TB at week 12.

Statistical analysis

A sample size of 419 subjects with previous TNF inhibitor use (335 CZP *vs* 84 placebo, with a 4:1 randomization) was expected to achieve at least 90% power to show a statistically significant difference in the proportion of ACR20 responders at week 12 between the CZP and placebo groups. This assumed a 30% and at least a 50% ACR20 response rate in the placebo and CZP groups, respectively. Assuming that the 419 subjects with previous anti-TNF use recruited in this study would represent 40% of the overall population, a total of 1048 subjects were required to be randomized (838 CZP *vs* 210 placebo).

Efficacy analysis was conducted on the intention-to-treat (ITT) population (all randomized patients). Primary efficacy analysis used non-responder imputation (e.g. patients with missing ACR20 response data at week 12, for any reason, were designated non-responders). Treatment comparisons were performed using logistic regression with factors for treatment, concomitant use of MTX at baseline, previous TNF inhibitor use and disease duration (<2 *vs* $\geqslant 2$ years). Treatment effects were estimated with odds ratios and 95% two-sided CIs obtained by fitting this model. Primary efficacy analysis was also conducted in the per-protocol subset using the same method as in the ITT population, if >15% of the ITT population had at least one major protocol deviation.

For the analysis of secondary categorical endpoints in the ITT population, treatment comparisons were performed with the logistic regression model used for the primary efficacy analysis. Treatment comparisons for change from baseline at week 12 in ACR components were analysed using an analysis of covariance model with the same factors as for the primary efficacy model and baseline values as covariates.

For continuous data, missing data were imputed by last observation carried forward analysis. Data were analysed separately in each stratification subgroup (concomitant use of MTX at baseline, previous TNF inhibitor use and disease duration). Tests of interaction between treatment and each stratification variable were conducted separately at the 5% significance level to examine whether treatment differences changed between each level of the assessed stratification variable. A significant interaction result implied that the treatment effect size (for the response variable) was influenced by the status of the assessed stratification variable.

The safety analysis was conducted on all patients who received treatment. AEs were summarized using the Medical Dictionary for Regulatory Activities (MeDRA) coding terms. Injection reactions were assessed as a special group of AEs and classified as injection-site reactions or systemic reactions (acute or delayed). AEs leading to SAEs, withdrawal or death were also assessed. SAEs based on exposure analysis (each person was counted once based on the first occurrence of the AE) were evaluated.

Results

Patients

A total of 1063 patients were randomized, and 771 (90.6%) in the CZP group and 184 (86.8%) in the placebo group completed the 12-week, double-blind phase; all those completing this phase of the study entered an open-label study (Fig. 1). Deviations from the protocol leading to exclusion from the per-protocol population occurred in 268 patients (25.2%): 222 (26.1%) in the CZP group and 46 (21.7%) in the placebo group. There are no clinical or demographic features in the protocol violator group that could have biased the overall findings. Baseline demographics and disease characteristics were similar between the groups (Table 1).

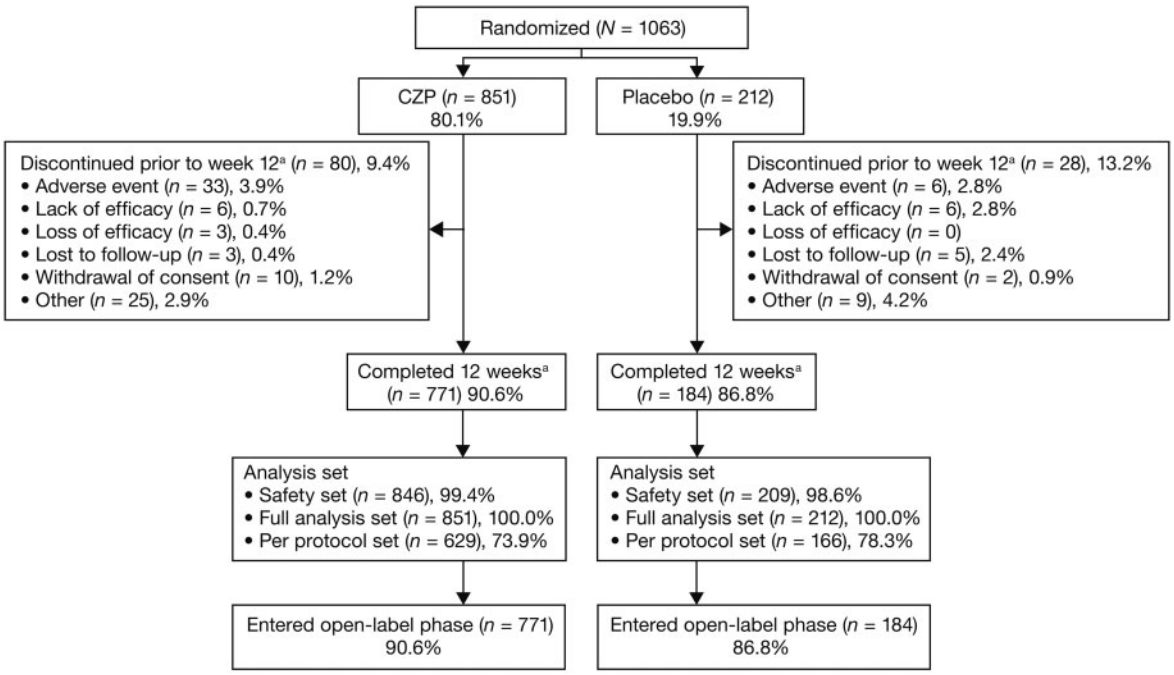
Treatment efficacy (ITT population)

At week 12, ACR20 response rates were 51.1% for the CZP group compared with 25.9% for placebo ($P < 0.001$). Similarly, the ACR50 and ACR70 response rates were 26.6 and 12.9% for the CZP group compared with 9.9 and 2.8% for placebo, respectively ($P < 0.001$ for each comparison) (Fig. 2A). The onset of treatment effect with CZP was rapid. ACR20 response rates were significantly higher in the CZP group compared with placebo as early as the first assessment at week 2 and at weeks 6 and 12 ($P < 0.001$ for each comparison) (Fig. 2B). Similarly, significantly more CZP patients achieved ACR50 response rates as early as week 2 onwards compared with placebo (CZP *vs* placebo: week 2, 9.6 *vs* 1.4%; week 6, 22.0 *vs* 4.7%; week 12, 26.6 *vs* 9.9%; $P < 0.001$ for each comparison). ACR70 response rates were higher at weeks 2, 6 and 12 compared with placebo [CZP *vs* placebo: week 2, 2.6 *vs* 0.5% ($P = 0.092$); week 6, 8.0 *vs* 0.9% ($P = 0.002$); week 12, 12.9 *vs* 2.8% ($P < 0.001$)]. Results in the per-protocol population were similar to the ITT population: 54.4% of CZP and 27.1% of placebo patients achieved an ACR20 response, 28.8% of CZP and 10.2% of placebo patients achieved an ACR50 response and 14.3% of CZP and 2.4% of placebo patients achieved an ACR70 response at week 12 ($P < 0.001$ for all comparisons).

Improvements in DAS28(CRP) were significantly higher in the CZP group from week 2 onwards compared with placebo ($P < 0.001$ for each comparison) (Table 2). Similarly, improvements in DAS28(ESR) were significantly higher in the CZP group from week 2 onwards (*post hoc* analysis) (Fig. 2C). For patients treated with CZP, 81.1% of patients achieved a DAS28(ESR) improvement of at least 1.2 up to week 12 *vs* 56.5% with placebo. DAS28(CRP) remission (<2.6) was seen in 16.0% of patients treated with CZP at week 12 compared with 5.7% of patients treated in the placebo group. Improvements in physical function were greater in patients with CZP treatment at weeks 2, 6 and 12 *vs* placebo ($P < 0.001$ for each comparison) (Fig. 2D).

Changes from baseline in each component of the ACR core set of disease activity measures were superior in the

FIG. 1 Patient disposition (ITT population).



[a]Double-blind phase.

CZP group compared with placebo and were significant from the first time point at week 2 (Table 3). At week 12, the mean change in HAQ-DI was −0.43 in the CZP group *vs* −0.21 with placebo ($P < 0.001$), and 56.4% of CZP patients met the minimal clinically important difference for HAQ-DI (improvement of at least 0.22 units) compared with 37.7% of PBO patients.

Analyses by pre-specified baseline stratification factors

Treatment efficacy with CZP was consistent across the subgroups stratified by previous TNF inhibitor use, concomitant use of MTX and disease duration. Week 12 ACR20 response rates were higher in CZP patients with and without previous TNF inhibitor use compared with placebo (with previous TNF inhibitor use: $P = 0.002$; without previous TNF inhibitor use: $P < 0.001$) (Table 2).

In *post hoc* analyses of clinical responses in patients with and without previous TNF inhibitor use, CZP-treated patients achieved higher ACR50/70 response rates and greater improvements in DAS28(ESR), DAS28(CRP) (Table 2) and physical function (HAQ-DI) compared with placebo (data not shown). ACR20 response rates were similar among CZP patients, irrespective of whether they discontinued TNF inhibitors for reasons of efficacy (49.7%) or non-efficacy (44.3%), and similar proportions of CZP patients previously receiving one or two TNF inhibitors achieved ACR20 response rates at week 12 (Table 2), regardless of whether they received adalimumab (45.0%), etanercept (52.4%) or infliximab (46.4%). ACR20 response rates were numerically higher in patients without previous TNF inhibitor use than in those with previous TNF inhibitor use, although the treatment interactions were not significant (NS) (interaction P = NS). The interaction was significant (interaction $P < 0.05$) for DAS28(CRP) and HAQ-DI in patients with previous TNF inhibitor use.

ACR20 response rates at week 12 were higher in the CZP group with or without concomitant MTX use at baseline compared with placebo, with significant differences in responses ($P < 0.001$ for each comparison). Week 12 ACR20 response rates were also higher in CZP patients, regardless of disease duration, compared with placebo (<2 years $P = 0.012$; ⩾2 years $P < 0.001$) (Table 2). In *post hoc* analyses, week 12 ACR50/70 response rates and DAS28(ESR) and DAS28(CRP) improvements were higher in CZP patients compared with placebo in the subgroups with or without concomitant MTX use at baseline, irrespective of disease duration (Table 2).

Post hoc subgroup analyses

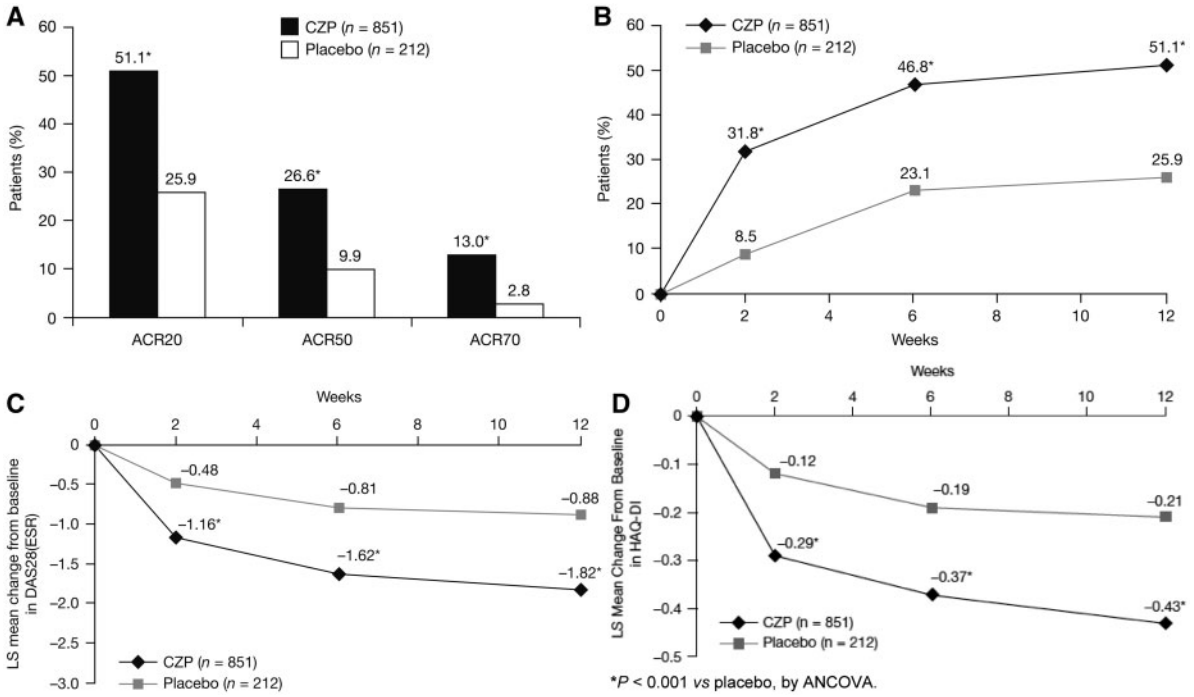
Post hoc analyses were conducted in additional subgroups of patients. ACR20 response rates at week 12 were similar in patients receiving monotherapy or combination DMARDs, regardless of whether the patients received one or two or more DMARDs or the type of concomitant DMARDs (Table 2). ACR50/70 response rates, DAS28(ESR) and DAS28(CRP) improvements were similar across the subgroups (Table 2). The interaction effects were non-significant for ACR20/50/70 responses

Table 1 Patient demographics and disease characteristics (ITT population)

	CZP[a] (*n* = 851)	Placebo (*n* = 212)
Patient demographics		
Age, mean (S.D.), years	55.4 (12.4)	53.9 (12.7)
Gender, % female	77.6	79.7
Duration, years		
Mean (S.D.)[b]	8.6 (8.8)	8.9 (9.1)
Median (interquartile range)[b]	5.4 (2.1–12.5)	6.3 (2.0–12.5)
Duration <2 years, *n* (%)	206 (24.2)	50 (23.6)
TJC, mean (S.D.)[c]	14.7 (6.6)	14.7 (6.6)
SJC, mean (S.D.)[c]	11.8 (5.6)	11.1 (5.2)
HAQ-DI, mean (S.D.)	1.5 (0.6)	1.6 (0.6)
DAS28(CRP), mean (S.D.)	5.7 (0.9)	5.7 (0.9)
DAS28(ESR), mean (S.D.)	6.4 (0.9)	6.4 (0.9)
CRP, mg/l; median (Q1, Q3)	9.0 (1.0, 164.0)	10.0 (2.9, 159.0)
ESR, mm/h; median (Q1, Q3)	37.0 (0, 140.0)	40.0 (10.0, 129.0)
RF-positive, ⩾14 IU/ml, *n* (%)	555 (73.9)	137 (76.5)
Positive anti-CCP antibody levels, *n* (%)	486 (65.9)	122 (67.8)
Median (Q1, Q3)	48.0 (0.9–800.1)	52.0 (0.9–800.1)
Treatment history		
MTX use at baseline, *n* (%)[d]	589 (69.2)	143 (67.5)
Mean (S.D.) dose, mg/week	17.2 (5.7)	16.6 (5.3)
Concomitant DMARD use, *n* (%)[e]	697 (81.9)	165 (77.8)
Number of concomitant DMARDs at baseline, *n* (%)[e]		
0	154 (18.1)	47 (22.2)
1	585 (68.7)	145 (68.4)
⩾2	112 (13.2)	20 (9.4)
Types of other concomitant DMARDs used, *n* (%)[e]		
LEF	80 (9.4)	15 (7.1)
SSZ	55 (6.5)	14 (6.6)
HCQ	98 (11.5)	16 (7.5)
Total number of prior DMARDs previously exposed to (including concomitant DMARDs at baseline), *n* (%)		
1	201 (23.6)	59 (27.8)
2	257 (30.2)	66 (31.1)
⩾3	391 (45.9)	85 (40.1)
Unknown	2 (0.2)	2 (0.9)
Previous TNF inhibitor use, *n* (%)[f]	320 (37.6)	80 (37.7)
Number of previous TNF inhibitor use, *n* (%)		
0	538 (63.2)	133 (62.7)
1	227 (26.7)	62 (29.2)
⩾2	86 (10.1)	17 (8.0)
Type of previous TNF inhibitor use, *n* (%)		
Adalimumab	111 (13.0)	38 (17.9)
Etanercept	164 (19.3)	31 (14.6)
Infliximab	109 (12.8)	27 (12.7)
Reasons for discontinuation of previous TNF inhibitors, *n* (%)		
Efficacy reasons	173 (20.3)	46 (21.7)
Non-efficacy reasons	140 (16.5)	33 (15.6)
Prior other biologic use, *n* (%)[g]	46 (5.4)	10 (4.7)
Concomitant CS use (systemic), *n* (%)	457 (53.7)	115 (54.2)
Median (Q1, Q3) dose, mg/day	5.0 (0.7–7500.0)	7.5 (2.0–30.0)

[a]CZP dose: 400 mg at weeks 0, 2 and 4; 200 mg at weeks 6, 8 and 10. [b]Duration at screening visit. [c]Assessment based on 28 joints. [d]Patients not taking MTX were permitted to take other DMARDs. [e]Ongoing at screening or taken during the study. [f]Based on the stratification flag. [g]Patients taking biologics within 2 months before baseline visit were excluded. TJC: tender joint count; SJC: swollen joint count.

FIG. 2 ACR response rates, DAS28(ESR) and HAQ-DI at week 12.



(**A**) ACR20/50/70 responder rates at week 12 [ITT population, non-responder imputation (NRI)]. *$P < 0.001$ *vs* placebo, by logistic regression. (**B**) ACR20 response rates up to week 12 (ITT population, NRI). *$P < 0.001$ *vs* placebo, by logistic regression. (**C**) DAS28(ESR) up to week 12 [ITT population, last observation carried forward (LOCF)]. *$P < 0.001$ *vs* placebo, by analysis of covariance (ANCOVA). (**D**) HAQ-DI up to week 12 (ITT population, LOCF). *$P < 0.001$ *vs* placebo, by ANCOVA.

and DAS28(ESR) and DAS28(CRP) values between the monotherapy and concomitant DMARD subgroups. ACR20 response rates at week 12 were similar in CZP patients having received one, two or three or more previous DMARDs (Table 2). In patients with MTX use at baseline but no previous TNF inhibitors, ACR20/50/70 response rates and DAS28(ESR) and DAS28(CRP) improvements were greater in the CZP group compared with placebo (Table 2).

ACR20 response rates were 53.2% for CZP patients with RF-positive status compared with 25.5% for placebo and 43.9% for CZP patients with RF-negative status (placebo, 31.0%) at baseline. The corresponding ACR50 and ACR70 response rates for CZP patients with RF-positive status were 27.9% and 13.3%, respectively (*vs* 10.2 and 3.6% for placebo), and 20.4% and 11.2%, respectively, for CZP patients with RF-negative status (9.5% and 2.4% placebo). The interaction effects were non-significant. Consistent efficacy was also observed among CZP patients grouped according to geographic region or baseline disease activity [DAS28(CRP) $\leqslant 5.1$ or >5.1] (data not shown).

Safety up to week 12

The incidence of AEs was comparable between the CZP and placebo groups (67.5% *vs* 61.7%, Table 4). The majority of AEs in both groups were of mild to moderate intensity. The most common AEs reported were nausea, upper respiratory tract infections, flare of RA and headaches (Table 4). Injection and infusion-site reactions occurred in 49 (5.8%) CZP and 2 (1.0%) placebo patients.

SAEs were reported in 52 patients (6.1%) in the CZP group and 12 (5.7%) in the placebo group during the double-blind phase of the study. The most common SAEs were infections occurring in 22 (2.6%) CZP patients and four (1.9%) placebo patients. Of these, the most common serious infections were lower respiratory tract and lung infections reported in seven (0.8%) CZP patients and one (0.5%) placebo patient. Two cases of *Aspergillus* were reported in the CZP group. As detailed in the Materials and methods section of this article, standard exclusion criteria for TB in trials of biologic agents were applied. There were no reported cases of TB in either group. There were four (0.5%) reported cases of malignant neoplasms in the CZP group (one case each of carcinoid tumour, adenocarcinoma of the pancreas, skin melanoma and uterine sarcoma) and two (1.0%) in the placebo group (one case each of breast cancer and skin melanoma).

AEs leading to permanent withdrawal from the study were reported in 40 (4.7%) CZP patients and eight (3.8%) placebo patients.

Table 2 Efficacy outcomes at week 12, CZP *vs* placebo

Patient group	ACR20, % responders		ACR50, % responders		ACR70, % responders		LS mean change from baseline in DAS28(ESR)		LS mean change from baseline in DAS28(CRP)	
	CZP	Placebo	CZP	Placebo	CZP	Placebo	CZP	Placebo	CZP	Placebo
ITT population (CZP = 851 *vs* placebo = 212)	51.1*,[a]	25.9	26.6*,[b]	9.9	12.9*,[b]	2.8	−1.82*	−0.88	−1.64*,[b]	−0.78
Stratification analyses										
Previous TNF inhibitor use[c] (CZP = 320 *vs* placebo = 80)	47.2**,[b]	27.5	21.6***	11.3	9.1****	3.8	−1.79	−1.13	−1.64	−1.02
No previous TNF inhibitor use[c] (CZP = 531 *vs* placebo = 132)	53.5*,[b]	25.0	29.6*	9.1	15.3*	2.3	−1.91	−0.80	−1.73	−0.73
Baseline MTX use										
Yes (CZP = 589 *vs* placebo = 143)	52.5*,[b]	28.0	28.4*	9.8	14.9*	3.5	−1.92	−0.90	−1.70	−0.80
No (CZP = 262 *vs* placebo = 69)	48.1*,[b]	21.7	22.5***	10.1	8.4****	1.4	−1.69	−0.93	−1.58	−0.83
Disease duration										
<2 years (CZP = 206 *vs* placebo = 50)	50.0***,[b]	30.0	26.7****	16.0	16.0***	4.0	−1.82	−0.94	−1.70	−0.90
⩾2 years (CZP = 645 *vs* placebo = 162)	51.5*,[b]	24.7	26.5*	8.0	11.9*	2.5	−1.66	−0.82	−1.67	−0.79
Post hoc subgroup analyses										
MTX use at baseline with no previous TNF inhibitor use (CZP = 377 vs placebo = 90)	55.2	28.9	31.3	10.0	17.5	3.3	−2.00	−0.84	−1.79	−0.76
Number of previous TNF inhibitors used										
1 (CZP = 227 *vs* placebo = 62)	46.7	30.6	20.7	14.5	9.7	4.8	−1.79	−1.25	−1.62	−1.08
2 (CZP = 85 *vs* placebo = 16)	48.2	12.5	22.4	0	7.1	0	−2.08	−0.86	−1.99	−0.93
Number of concomitant DMARDs[d] at baseline										
0 CZP monotherapy (CZP = 154 *vs* placebo = 47)	46.1	21.3	22.1	12.8	8.4	2.1	−2.22	−1.41	−2.09	−1.25
1 (CZP = 585 *vs* placebo = 145)	52.0	26.9	26.7	9.0	13.8	2.8	−1.82	−0.85	−1.63	−0.76
⩾2 (CZP = 112 *vs* placebo = 20)	53.6	30.0	32.1	10.0	14.3	5.0	−1.74	−0.85	−1.57	−0.77
Type of concomitant DMARDs										
MTX (CZP = 582 *vs* placebo = 140)	52.4	27.1	28.4	8.6	14.9	3.6	−1.91	−0.88	−1.69	−0.77
LEF[e] (CZP = 79 *vs* placebo = 15)	55.7	13.3	26.6	6.7	8.9	0	−1.92	−0.95	−1.77	−0.83
SSZ[e] (CZP = 53 *vs* placebo = 13)	56.6	30.8	24.5	15.4	9.4	7.7	−1.94	−1.30	−1.83	−1.24
HCQ[e] (CZP = 93 *vs* placebo = 16)	45.2	37.5	25.8	12.5	10.8	0	−1.67	−0.84	−1.50	−0.89

[a]Primary endpoint. [b]Secondary endpoint. [c]Interaction P = non-significant for ACR20/50/70 responses; interaction $P < 0.05$ for DAS28(CRP). [d]Interaction P = non-significant for all clinical responses. Treatment effect differences between subgroups were assessed by interactions at the 5% significance level. P-values are reported for all clinical responses for the ITT population and for differences in ACR20/50/70 responses between placebo and CZP for pre-specified stratification analyses. Interactions are reported for subgroup analyses to test for consistency of efficacy across subgroups. P-values are not reported for *post hoc* analyses. ACR responses were determined using non-responder imputation, and DAS28(CRP) and DAS28(ESR) values were determined using last observation carried forward. [e]Patients may have received more than one DMARD, e.g. LEF + MTX. *$P < 0.001$; **$P < 0.01$; ***$P < 0.05$; ****P = not significant *vs* placebo, by logistic regression. LS: least squares.

TABLE 3 Change from baseline in individual ACR core components at weeks 2, 6 and 12 (ITT population, LOCF)

ACR core components, least square mean (S.E.)	Week 2		Week 6		Week 12	
	CZP[a] ($n = 851$)	Placebo ($n = 212$)	CZP[a] ($n = 851$)	Placebo ($n = 212$)	CZP[a] ($n = 851$)	Placebo ($n = 212$)
TJC	−4.3* (0.24)	−2.7 (0.41)	−6.3* (0.27)	−4.1(0.46)	−7.3* (0.28)	−4.4 (0.48)
SJC	−3.9* (0.19)	−2.1 (0.32)	−5.7* (0.19)	−3.4 (0.33)	−6.1* (0.21)	−3.7 (0.36)
Patient's assessment of arthritis pain (VAS)	−15.5* (0.95)	−3.0 (1.62)	−18.6* (1.03)	−8.2 (1.77)	−21.1* (1.09)	−7.9 (1.86)
Patient's global assessment of disease activity (VAS)	−14.9* (0.94)	−2.6 (1.61)	−17.9* (1.00)	−7.6 (1.72)	−20.4* (1.06)	−7.7 (1.81)
Physician's global assessment of disease activity (VAS)	−19.1* (0.84)	−10.0 (1.44)	−26.2* (0.90)	−14.8 (1.54)	−29.6* (0.96)	−17.5 (1.63)
HAQ-DI	−0.29* (0.02)	−0.12 (0.03)	−0.37* (0.02)	−0.19 (0.04)	−0.43* (0.02)	−0.21 (0.04)
CRP LS geometric mean (95% CI)—ratio to baseline	0.50* (0.47–0.53)	1.07 (0.98–1.18)	0.54* (0.50–0.57)	1.02 (0.92–1.13)	0.57* (0.53–0.61)	1.10 (0.98–1.22)

[a]CZP dose: 400 mg at weeks 0, 2 and 4; 200 mg at weeks 6, 8 and 10. *$P < 0.001$ *vs* placebo, by ANCOVA. ANCOVA: analysis of covariance; LOCF: last observation carried forward; TJC: tender joint count; SJC: swollen joint count; VAS: visual analogue scale.

There were two deaths in the CZP group: one case of sigmoid diverticulitis in a 73-year-old man with pancreatitis, which occurred 56 days after first CZP dose, and one of necrotizing pneumonia, which occurred 20 days after the first CZP dose in a 63-year-old man with diabetes who was treated with CSs and refused hospitalization. Both deaths were ruled as possibly related to CZP.

Discussion

In this 12-week randomized controlled study, the addition of CZP to current therapy was associated with a rapid and consistent clinical response in a diverse clinically representative group of patients with active RA, with different disease durations and a broad range of previous and current medications, including previous TNF inhibitor use. To our knowledge, no clinical studies have examined the benefits of treatment with a TNF inhibitor in RA patients taking DMARDs other than MTX within the context of a single, placebo-controlled, randomized trial. These findings expand previous observations about CZP, demonstrating its efficacy and safety in a wider group of patients that more closely resemble those seen in routine clinical practice.

The beneficial effects of CZP occurred as early as the first assessment at week 2 for primary and most secondary efficacy endpoints. The rapid onset of response was consistent with findings from the RAPID 1 and 2 (phase III studies of CZP add-on to MTX *vs* MTX plus placebo) and FAST4WARD (monotherapy with CZP) studies in which clinical benefits were achieved as early as the first assessment at week 1 of treatment with CZP [7–9]. In this study, robust and significant improvements were observed both in disease activity and physical function.

Treatment with CZP was associated with significantly higher ACR20 and ACR50 response rates at week 12 in patients with or without previous TNF inhibitor use compared with placebo. Although the efficacy of CZP in patients without previous use of TNF inhibitors [7–9] was confirmed, the current study extends these observations to patients with previous TNF inhibitor use, regardless of the number or type of previous TNF inhibitors used.

Improvements in RA signs and symptoms after treatment with TNF inhibitors have been reported in patients who had previously received these agents [11, 12] and other biologics [13–15]. In this 12-week study, clinical responses were consistent across all subgroups irrespective of previous or concomitant therapy. Importantly, ACR response rates and improvements in DAS28(ESR), DAS28(CRP) and HAQ-DI were similar in patients receiving CZP as monotherapy or with concomitant DMARDs, regardless of the number or type of DMARDs.

Clinical response rates in this study are similar to those achieved at 12 weeks in other randomized trials such as the Rheumatoid Arthritis Prevention of Structural Damage 2 (RAPID 2) study where, after treatment with CZP in addition to MTX, ACR20/50/70 response rates were approximately 60%, 30% and 10%, respectively, in patients who had not received previous TNF inhibitors [8, 9]. In this study, week 12 ACR20/50/70 response rates

Table 4 Treatment-emergent AEs up to week 12 (safety population)

Exposure and adverse event	CZP[a] (*n* = 846)	Placebo (*n* = 209)
Duration of exposure, patient-years	196.4	48.9
Any AEs by maximum intensity, *n* (%)		
Mild	248 (29.3)	56 (26.8)
Moderate	257 (30.4)	58 (27.8)
Severe	66 (7.8)	15 (7.2)
AEs, incidence rate/100 patient-years (*n*, patient %)		
Any AEs[b]	522.1 (571, 67.5)	483.2 (129, 61.7)
Infections	143.9 (245, 29.0)	112.5 (48, 23.0)
Upper respiratory tract infections	59.3 (112, 13.2)	41.5 (19, 9.1)
Headaches NEC	24.2 (47, 5.6)	23.5 (11, 5.3)
Nausea and vomiting symptoms	21.5 (42, 5.0)	28.2 (13, 6.2)
Rheumatoid arthropathies	18.8 (37, 4.4)	37.0 (17, 8.1)
Serious AEs[c]	26.7 (52, 6.1)	25.8 (12, 5.7)
Serious infections	11.1 (22, 2.6)	8.3 (4, 1.9)
Lower respiratory tract and lung infections	3.5 (7, 0.8)	2.1 (1, 0.5)
Streptococcal infections	0 (0, 0)	2.1 (1, 0.5)
Urinary tract infections	2.5 (5, 0.6)	4.2 (2, 1.0)
Death	1.0 (2, 0.2)	0 (0, 0)
AEs leading to withdrawal	20.6 (40, 4.7)	17.1 (8, 3.8)
Injection and infusion site reactions	25.3 (49, 5.8)	4.2 (2, 1.0)

[a]CZP dose: 400 mg at weeks 0, 2 and 4; 200 mg at weeks 6, 8 and 10. [b]AEs occurring in >5.0% of patients in either treatment group are presented below the column subheading Any AEs in the table. [c]Any important medical event including events that do not require hospitalization, such as certain opportunistic infections. NEC: not elsewhere classified.

were similar (55.1% *vs* 31.3% *vs* 17.6%) in a comparable subgroup of CZP patients with MTX use (and other concomitant DMARD use) at baseline and no previous use of TNF inhibitors.

The safety and tolerability profile of CZP in this study was consistent with that in previous CZP trials [7–9], studies with other TNF inhibitors [16, 17] and previous studies of a second TNF inhibitor initiated after the failure of a first biologic agent [18–20]. There were no reported cases of TB in either the CZP or placebo group. The demonstrated efficacy and safety at 12 weeks after CZP therapy suggest a favourable risk–benefit profile for patients.

Limitations of this study include its short 12-week duration and a lack of radiographic assessment. Longer-term evaluations in the open-label phase will further characterize the safety profile of CZP in this heterogeneous population. Additionally, patients treated with more than two TNF inhibitors or rituximab and/or abatacept were excluded, and a washout period was required for patients using biologics. Therefore, the results are not relevant to these groups.

In conclusion, after 12 weeks, treatment with CZP both as monotherapy or with concomitant DMARDs was associated with rapid and consistent clinical responses reducing disease activity and improving physical function in patients with or without previous TNF inhibitor use, regardless of their baseline MTX use or disease duration. These findings suggest that CZP is effective in a broad, clinically relevant population of patients with active RA.

Rheumatology key messages

- Clinical trials often comprise homogeneous patient populations that may not reflect patients in clinical care.
- The REALISTIC study evaluated CZP in a broad RA population resembling patients seen in clinic.
- CZP resulted in rapid and consistent clinical responses in a diverse group of RA patients.

Acknowledgements

The authors thank all the investigators and patients who participated in this study. They also thank Marine Champsaur from UCB Pharma for critical review of the manuscript. They acknowledge the editorial services of Jaya Kolipaka and Andrew Richardson from PAREXEL, which were funded by UCB Pharma. UCB Pharma was involved in the study design, collection, analysis and interpretation of data.

Funding: This work was supported by UCB Pharma.

Disclosure statement: M.D. has received research grants and consulting fees from Abbott Laboratories, Bristol-Myers Squibb, Pfizer, Roche and UCB Pharma. T.W.J.H. has received consulting fees from UCB Pharma. R.F.v.V. has received research grants and consulting fees from UCB Pharma. C.O.B. has served as an investigator and received consulting fees from UCB Pharma. J.P. has

received research grants and consulting fees from UCB Pharma, Abbott Laboratories, Actelion, Amgen, AstraZeneca, Bristol-Myers Squibb, Genentech, GlaxoSmithKline, Johnson & Johnson, MedImmune, Merck, Novartis, Pfizer, Roche, Sanofi, Sorono, Teva and United Therapeutics. N.G. is a former employee of UCB Pharma and is currently an employee of Quintiles. N.G. owns UCB Pharma stock. R.F. has received research grants and consulting fees from UCB Pharma. M.E.W. has received research grants from Abbott, Bristol-Myers Squibb, Roche, Biogen/Idec, Medimmune, Cresendo Bioscience and UCB Pharma, and consulting fees from UCB Pharma, Abbott Laboratories, Amgen, Bristol-Myers Squibb, Roche, Biogen/Idec, Medimmune, Cresendo Bioscience Pfizer and Centocor. J.W. has received consultancy fees from, and participated in a speakers bureau for, UCB Pharma. O.D. is a UCB Pharma employee and has stocks, stock options or bond holdings in UCB Pharma. P.E. has received research grants and consulting fees from Pfizer, Merck, Abbott Laboratories, Roche, Bristol-Myers Squibb and UCB Pharma. B.D. is a UCB Pharma employee and owns UCB Pharma stock. E.M. has received consulting fees from UCB Pharma, Amplimmune, Constellation Pharmaceuticals and Wachovia; has worked as an investigator for Bristol-Myers Squibb and Roche; and has received honorarium from the ACR and Up to Date.

References

1 Keystone EC, Genovese MC, Klareskog L *et al*. Golimumab, a human antibody to tumour necrosis factor α given by monthly subcutaneous injections, in active rheumatoid arthritis despite methotrexate therapy: the GO-FORWARD study. Ann Rheum Dis 2009;68:789–96.

2 Breedveld 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 previous methotrexate treatment. Arthritis Rheum 2006;54:26–37.

3 Klareskog L, van der Heijde D, de Jager JP *et al*. Therapeutic effect of the combination of etanercept and methotrexate compared with each treatment alone in patients with rheumatoid arthritis: double-blind randomised controlled trial. Lancet 2004;363:675–81.

4 Lipsky PE, van der Heijde DM, St Clair EW *et al*. Infliximab and methotrexate in the treatment of rheumatoid arthritis. N Engl J Med 2000;343:1594–602.

5 Sokka T, Pincus T. Most patients receiving routine care for rheumatoid arthritis in 2001 did not meet inclusion criteria for most recent clinical trials or American College of Rheumatology criteria for remission. J Rheumatol 2003; 30:1138–46.

6 Zink A, Strangfeld A, Schneider M *et al*. Effectiveness of tumor necrosis factor inhibitors in rheumatoid arthritis in an observational cohort study: comparison of patients according to their eligibility for major randomized clinical trials. Arthritis Rheum 2006;54:3399–407.

7 Fleischmann R, Vencovsky J, van Vollenhoven RF *et al*. Efficacy and safety of certolizumab pegol monotherapy every 4 weeks in patients with rheumatoid arthritis failing previous disease-modifying antirheumatic therapy: the FAST4WARD study. Ann Rheum Dis 2009;68: 805–11.

8 Keystone E, Heijde D, Mason D Jr *et al*. Certolizumab pegol plus methotrexate is significantly more effective than placebo plus methotrexate in active rheumatoid arthritis: findings of a fifty-two-week, phase III, multicenter, randomized, double-blind, placebo-controlled, parallel-group study. Arthritis Rheum 2008;58: 3319–29.

9 Smolen J, Landewé RB, Mease P *et al*. Efficacy and safety of certolizumab pegol plus methotrexate in active rheumatoid arthritis: the RAPID 2 study. A randomised controlled trial. Ann Rheum Dis 2009;68: 797–804.

10 Arnett FC, Edworthy SM, Bloch DA *et al*. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 1988; 31:315–24.

11 Smolen JS, Kay J, Doyle MK *et al*. Golimumab in patients with active rheumatoid arthritis after treatment with tumour necrosis factor alpha inhibitors (GO-AFTER study): a multicentre, randomised, double-blind, placebo-controlled, phase III trial. Lancet 2009;374: 210–21.

12 Furst DE, Schiff MH, Fleischmann RM *et al*. Adalimumab, a fully human anti tumor necrosis factor-alpha monoclonal antibody, and concomitant standard antirheumatic therapy for the treatment of rheumatoid arthritis: results of STAR (Safety Trial of Adalimumab in Rheumatoid Arthritis). J Rheumatol 2003;30:2563–71.

13 Cohen SB, Emery P, Greenwald MW *et al*. Rituximab for rheumatoid arthritis refractory to anti-tumor necrosis factor therapy: results of a multicenter, randomized, double-blind, placebo-controlled, phase III trial evaluating primary efficacy and safety at twenty-four weeks. Arthritis Rheum 2006;54:2793–806.

14 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.

15 Genovese MC, Becker JC, Schiff M *et al*. Abatacept for rheumatoid arthritis refractory to tumor necrosis factor alpha inhibition. N Engl J Med 2005;353: 1114–23.

16 Johnsen AK, Schiff MH, Mease PJ *et al*. Comparison of 2 doses of etanercept (50 vs 100 mg) in active rheumatoid arthritis: a randomized double blind study. J Rheumatol 2006;33:659–64.

17 van de Putte LB, Atkins C, Malaise M *et al*. Efficacy and safety of adalimumab as monotherapy in patients with rheumatoid arthritis for whom previous disease modifying antirheumatic drug treatment has failed. Ann Rheum Dis 2004;63:508–16.

18 van Vollenhoven R, Harju A, Brannemark S, Klareskog L. Treatment with infliximab (Remicade) when etanercept

(Enbrel) has failed or vice versa: data from the STURE registry showing that switching tumour necrosis factor alpha blockers can make sense. Ann Rheum Dis 2003;62:1195–8.

19 Brocq O, Albert C, Roux C, Gerard D, Breuil V, Ziegler LE. Adalimumab in rheumatoid arthritis after failed infliximab and/or etanercept therapy: experience with 18 patients. Joint Bone Spine 2004;71:601–3.

20 Gómez-Puerta JA, Sanmartí R, Rodríguez-Cros JR, Cañete JD. Etanercept is effective in patients with rheumatoid arthritis with no response to infliximab therapy. Ann Rheum Dis 2004;63:896.