Certolizumab pegol in rheumatoid arthritis: a review of Phase III clinical trials and its role in real-life clinical practice

Over the last decade, evidence has accumulated demonstrating the effectiveness of early suppression of inflammation in patients with rheumatoid arthritis. This is reflected in evidence-based guidelines recommending treatment according to a target of disease activity or patient function, the ultimate target being clinical remission. In the same period, an increasing number of biologic therapies have become available, providing multiple treatment options for patients failing conventional disease-modifying antirheumatic drugs. Recently two new TNF inhibitor agents have been licensed: certolizumab pegol and golimumab. This article will examine evidence of the efficacy and safety of certolizumab pegol in rheumatoid arthritis, its potential utility in the context of a market comprising multiple TNF inhibitor agents and where its use may be positioned in the future.

KEYWORDS: biologic therapy ■ remission ■ rheumatoid arthritis ■ TNF inhibitor

Sarah C Horton[1,2], Sudipto Das[1,2] & Paul Emery[†1,2]

[1]Section of Musculoskeletal Disease, Leeds Institute of Molecular Medicine, University of Leeds, UK
[2]NIHR Leeds Musculoskeletal Biomedical Research Unit, Leeds Teaching Hospitals NHS Trust, UK
[†]Author for correspondence:
Tel.: +44 113 392 4884
Fax: +44 113 392 4991
p.emery@leeds.ac.uk

TNF inhibitors (TNFi) have been in use in clinical practice for the treatment of rheumatoid arthritis (RA) since 1998. The first to be licensed was etanercept, a fusion protein consisting of two soluble p75-TNF-receptor domains and the constant fragment of immunoglobulin. Next was the chimeric mouse human antibody infliximab (the first TNFi to be trialed in man) and later the fully human antibody adalimumab. In patients with RA failing conventional disease-modifying antirheumatic drugs (DMARDs), randomized controlled trials demonstrated all three were effective, especially when used in combination with methotrexate (MTX) [1–3]. Significantly higher proportions of patients achieved clinical responses (as defined by the American College of Rheumatology [ACR] criteria) in comparison to placebo. For example, in the ATTRACT study (patients with active RA despite receiving MTX for at least 3 months) the proportion of patients responding to infliximab with MTX at 30 weeks was significant at ACR20 and ACR50 levels (50 and 27% achieved these levels of response, respectively) in comparison to placebo with MTX (20 and 5% achieving these levels) [2]. This illustrates that although infliximab is effective, response is far from universal in this patient group, with subsequent trials of infliximab and alternative TNFi agents consistently reporting at least 30% of patients fail to meet even the lowest threshold of a definition of response, a 20% improvement (ACR20). With the present ideal being to meet higher targets of treatment, with the ultimate goal being remission, there is a need for alternative treatment options. Furthermore, over time, patients may also lose their initial response to therapy. An observational study of initial responders to infliximab demonstrated that up to half of patients may develop secondary nonresponse within the first year of treatment [4].

The frequency of primary and secondary nonresponse has contributed to the perceived need for new agents. Thus there has been the development of a number of other biologic agents for use in RA including the new TNFi agents: certolizumab pegol (CZP) and golimumab. Experience [5] and randomized controlled trial data [6] have revealed that despite nonresponse to one TNFi agent, patients may respond to a second drug in this class, with TNFi agents possessing different pharmacokinetic properties and potentially different mechanisms of action. For example, the ability of etanercept to inhibit the action of lymphotoxin has been implicated as a mechanism for response to etanercept in a patient with resistance to infliximab [7]. Moreover, intolerance to TNFi therapy warranting cessation of treatment may be idiosyncratic (rather than a TNFi class effect) permitting use of an alternative TNFi. CZP has a unique structure, being a fragment of humanized monoclonal antibody and lacking the constant fragment of immunoglobulin (Fc). Thus, addition of CZP to the existing options for TNFi agents may therefore offer a significant alternative in clinical practice. In this article differences between CZP and other TNFi agents will be discussed.

future medicine part of fsg

Three pivotal Phase III clinical trials provide evidence for the efficacy and safety of CZP in RA, in patients for whom MTX or other conventional DMARDs have been ineffective [8–10]. On the basis of these trials, in 2009, CZP was approved for use in this patient group in the USA, Canada and Europe at a starting dose of 400 mg at weeks 0, 2 and 4, followed by 200 mg every 2 weeks for maintenance. US and Canadian authorization bodies also allow maintenance dosing at 400 mg every 4 weeks. It has been licensed both for use in combination with MTX, and as a biologic monotherapy in the case of intolerance to MTX or if use of MTX is clinically inappropriate.

Structure & mechanism of action

Certolizumab pegol is distinct from other TNFi in terms of its structure. It is composed of the antibody binding fragment (Fab) of humanized monoclonal antibody against TNF conjugated to polyethylene glycol; therefore, unlike other agents, it does not contain the constant fragment of immunoglobulin (Fc) (see Figure 1). Attachment of polyethylene glycol to Fab increases its plasma half-life to that comparable to whole antibody subcutaneous TNF inhibitors such as adalimumab, to approximately 14 days, allowing fortnightly subcutaneous administration.

Certolizumab pegol binds to soluble and membrane-bound TNF-α, inhibiting the proinflammatory actions of this cytokine. Unlike other TNFi, owing to its lack of the Fc component, it is incapable of fixing complement or binding to Fc receptors. It does not cause antibody-dependent or complement-dependent cytotoxicity *in vitro* unlike monoclonal antibodies, suggesting this mechanism of action may not be necessary for clinical efficacy of TNFi therapies in RA [11]. A study in mice with collagen-induced arthritis demonstrated that CZP penetrated inflamed joint tissue to a greater extent and for a longer time period than either adalimumab or infliximab and the degree of penetration correlated better with the level of inflammation within the tissue. Whether this corresponds to any patient benefit clinically is not known [12].

An additional *in vitro* property of CZP, of unknown clinical relevance as yet, is that it does not cross the placenta at a detectable level, unlike infliximab, which has been shown to cross the placenta with high levels evident in newborns [13]. This may be explained by the fact that, in the second trimester of pregnancy, IgG crosses the placenta via a process mediated through its Fc component. In addition, serum levels of CZP in infants born to mothers receiving CZP for inflammatory bowel disease suggest CZP is not actively transferred across the placenta in the third trimester of pregnancy [14].

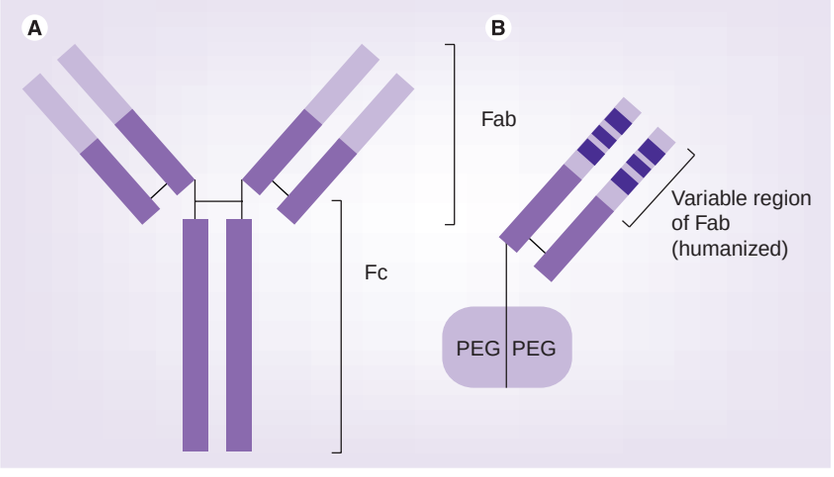

Figure 1. (A) The structure of a monoclonal antibody, such as infliximab, adalimumab or golimumab, and (B) the structure of certolizumab.
Fab: Antibody-binding fragment of immunoglobulin; Fc: Constant fragment.

Efficacy

A literature search was conducted in PubMed, EMBASE and the Cochrane Library for papers published up to and including January 2011, using the terms 'certolizumab' and 'RA' to identify relevant Phase III (or later) clinical trials. Abstracts from the annual meetings of the European League Against Rheumatism (2007–2011) and the American College of Rheumatology (2007–2010) were also searched. Efficacy in combination with MTX was assessed in the RAPID 1 and 2 trials [8,9]. Evidence for effectiveness as monotherapy, and 4-weekly administration, is provided by the FAST4WARD trial [10]. Baseline characteristics of patients across these studies are summarized in Table 1. Preliminary results of two Phase IIIb studies have also recently been published in abstract form.

Clinical efficacy: CZP in combination with MTX

In RAPID 1 [8] and 2 [9] trials, patients with active RA, despite at least 6 months of MTX therapy, were randomized 2:2:1 to CZP 200 or 400 mg every other week (with a loading dose in both groups of 400 mg at weeks 0, 2 and 4) or to placebo, with all groups receiving MTX. The trials differed in the formulation of CZP used (lyophilized form in RAPID 1 and

Table 1. Baseline demographics summary of Phase III studies†.

Characteristics†	RAPID 1 [8]			RAPID 2 [9]			FAST4WARD [10]	
	Placebo n = 199	*CZP 200 mg 2-weekly n = 393*	*CZP 400 mg 2-weekly n = 390*	*Placebo n = 127*	*CZP 200 mg 2-weekly n = 246*	*CZP 400 mg 2-weekly n = 246*	*Placebo n = 109*	*CZP 400 mg 4-weekly n = 111*
Age	52.2	51.4	52.4	51.5	52.2	51.9	54.9	52.7
Duration in years	6.2	6.1	6.2	5.6	6.1	6.5	10.4	8.7
Number of prior DMARDs	1.4	1.3	1.3	1.2	1.2	1.3	2.0	2.0
MTX dose (mg)	13.4	13.6	13.6	12.2	12.5	12.6	NA	NA
Tender joints	29.8	30.8	31.1	30.4	30.1	30.0	28.3	29.6
Swollen joints	21.2	21.7	21.5	21.9	20.5	21.0	19.9	21.2
Patient global assessment of arthritis VAS (mm)	64.2	63.1	64.1	59.9	62.4	61.1	3.3	3.3
ESR (mm/h)	45.0 (median)	43.5 (median)	42.5 (median)	40.8	43.7	39.1	35.6	30.9
DAS28	7	6.9	6.9	6.83	6.85	6.80	6.3 (based on three variables)	6.3 (based on three variables)

†All values are mean values except where median values have been reported, as indicated.
CZP: Certolizumab pegol; DAS28: Disease Activity Score (based on 28 joints); DMARD: Disease-modifying antirheumatic drug; ESR: Erythrocyte sedimentation rate; MTX: Methotrexate; NA: Not applicable; VAS: Visual Analog Scale.
RAPID 1 data reproduced with permission from [8] *© John Wiley and Sons.*
RAPID 2 data and FAST4WARD data reproduced with permission from [9,10] *© BMJ Publishing Group Ltd.*

liquid form in RAPID 2) and in the length of the study period (52 weeks in RAPID 1 and 24 weeks in RAPID 2). In both studies the primary end point was ACR20 response at 24 weeks, with an additional co-primary end point in RAPID 1: the mean change from baseline in the modified total Sharp score at week 52. In both studies, patients who did not achieve ACR20 response at week 12 and 14 were withdrawn and were offered CZP 400 mg every 2 weeks, open-label.

Treatment with CZP plus MTX significantly reduced the signs and symptoms of RA as compared with placebo plus MTX. Response rates are displayed in Table 2; at week 24 in RAPID 1, ACR response rates for the groups taking 200 and 400 mg of CZP plus MTX were 59 and 61%, respectively, compared with 14% for the placebo plus MTX group ($p < 0.001$ for each comparison). These results are similar to those seen in RAPID 2. Significantly higher numbers of patients achieved the secondary end points ACR50 and ACR70, and RAPID 1 demonstrated that response rates were maintained through to week 52 (Figure 2 shows response rates at study end points i.e., at week 52 in RAPID 1 and week 24 in RAPID 2).

Effects were seen as early as week 1 (23% of patients receiving 200 mg CZP vs 6% of controls achieved ACR20 response in CZP-treated groups in RAPID 1), peaked at week 12 and then plateaued with response rates sustained until the study end [15]. Further *post-hoc* analysis of RAPID 1 data (including its open-label extension) has confirmed response within the first 12 weeks of treatment determines the likelihood of achieving a good long-term response; if reduction in DAS28 score was less than 1.8 from baseline to week 12, patients had a less than 5% chance of achieving low disease activity (determined by DAS28 ≤3.2) at 1 and 2 years [16]. Long-term efficacy of CZP has also been demonstrated from data of a 3-year open-label extension of the RAPID 2 trial. Of the 342 patients receiving open-label CZP (400 mg every other week) and MTX, only two withdrew due to lack of efficacy and ACR responses were maintained [17].

Clinical efficacy: CZP monotherapy

In the FAST4WARD trial, 220 patients with active RA, who had failed one or more DMARD therapies, were randomized 1:1 to 400 mg CZP or placebo every 4 weeks [10]. The primary outcome, ACR20 response at week 24,

Table 2. The percentage of patients achieving levels of response defined by the American College of Rheumatology (ACR20, ACR50 and ACR70) at 24 weeks.

	RAPID 1 [8]			RAPID 2 [9]			FAST4WARD [10]	
	Placebo + MTX n = 199	*CZP 200 mg 2-weekly + MTX n = 393*	*CZP 400 mg 2-weekly + MTX n = 390*	*Placebo + MTX n = 127*	*CZP 200 mg 2-weekly + MTX n = 246*	*CZP 400 mg 2-weekly + MTX n = 246*	*Placebo n = 109*	*CZP 400 mg 4-weekly n = 111*
ACR20 (%)	13.6	58.8 p < 0.001	60.8 p < 0.001	8.7	57.3 p < 0.001	57.6 p < 0.001	9.3	45.5 p < 0.001
ACR50 (%)	7.6	37.1 p < 0.001	39.9 p < 0.001	3.1	32.5 p < 0.001	33.1 p < 0.001	3.7	22.7 p < 0.001
ACR70 (%)	3.0	21.4 p < 0.001	20.6 p < 0.001	0.8	15.9 p < 0.001	10.6 p ≤ 0.01	0.0	5.5 p ≤ 0.05

p-values are provided for active treatment groups in comparison to placebo groups, in an intention-to-treat population in RAPID 1 and RAPID 2 and modified intention-to-treat population in FAST4WARD.
ACR: American College of Rheumatology; CZP: Certolizumab pegol; MTX: Methotrexate.

was achieved in 46% of CZP-treated patients compared with 9% of controls (p < 0.001). ACR50 and ACR70 responses were also superior in the CZP group (see Table 2 & Figure 3). Effects on measures of disease activity were seen as early as week 1: least squares mean change from baseline in swollen and tender joint counts were 6 and 10, respectively, in CZP groups, compared with more moderate improvements observed in controls (3 and 5; p < 0.001 for both comparisons).

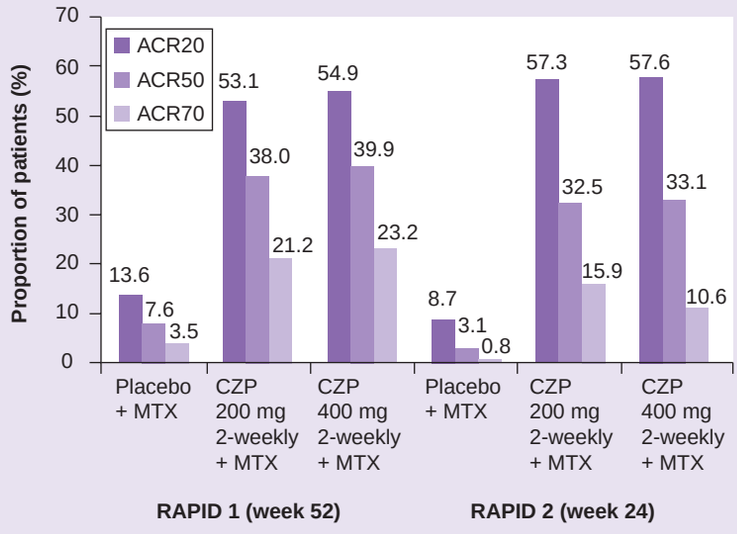

Figure 2. Proportion of patients achieving levels of response defined by the American College of Rheumatology (ACR20, ACR50 and ACR70) with combination certolizumab pegol and methotrexate in RAPID 1 and 2 trials at the end of the randomized study periods.
ACR: American College of Rheumatology; CZP: Certolizumab pegol; MTX: Methotrexate.
RAPID 1 data reproduced with permission from [8] © John Wiley and Sons.
RAPID 2 data reproduced with permission from [9] © BMJ Publishing Group Ltd.

Clinical efficacy: Phase IIIb studies

The REALISTIC trial aimed to assess CZP efficacy in patients with active RA (despite treatment with at least one DMARD) with characteristics more reflective of every day practice [18]. Patients were randomized to receive CZP (n = 851) or placebo (n = 212) whilst continuing their current therapy, and were stratified according to concomitant use of MTX, prior TNFi use and disease duration. A significant difference in the primary outcome, ACR20 response at 12 weeks, was observed with 51% of CZP-treated patients responding in comparison to 26% of controls. The proportion of patients previously treated with a TNFi was 38%. ACR20 response rates at week 12 were comparable regardless of disease duration (<2 years compared with 2 years or more), whether patients were receiving concomitant DMARDs or had received prior TNFi. ACR20 response rates for patients receiving CZP monotherapy were 47% (n = 168) versus 21% in controls (n = 48), and for patients receiving CZP with one concomitant DMARD were 52% (n = 574) versus 28% (n = 144) in controls. Rates for patients with prior TNFi exposure were 47% (n = 320) versus 28% in controls (n = 80), and for patients who were TNFi naive were 54% (n = 531) versus 25% (n = 132) in controls, with similar response rates seen in those discontinuing prior TNFi due to intolerance or inefficacy [19].

The CERTAIN trial evaluated induction of remission with CZP in comparison to placebo in 194 patients with low or moderate disease activity (defined by Clinical Disease Activity Index [CDAI]) on DMARD therapy [20]. The primary end point, remission at week 20 and 24 (defined by CDAI) was met, being achieved in 19% of CZP-treated patients versus 7% of

controls ($p < 0.05$). Other findings included fewer CZP-treated patients having moderate or high disease activity at 24 weeks in comparison to controls (37 vs 70%; $p < 0.001$).

Radiographic outcomes

Evaluation of radiographic data in RAPID 1 demonstrated prevention of progression of structural damage with CZP and MTX: at 52 weeks the mean change from baseline in modified total Sharp score was significantly lower in patients treated with CZP regimens compared with placebo, with no significant difference between the two CZP dose groups (mean change 0.4 in patients receiving CZP 200 mg vs 2.8 receiving MTX alone, $p < 0.001$) [8]. In addition, in RAPID 2, the mean change in van der Heijde modified total Sharp score from baseline at week 24 was lower in the treatment arm compared with placebo (0.2 vs 1.2; $p < 0.01$) [9]. Radiographic data were not assessed for CZP monotherapy in the FAST4WARD study.

Analysis of radiographic progression in patients who withdrew from either RAPID trial at week 16 (failing to meet ACR20 criteria at weeks 12 and 14) revealed significantly less radiographic progression in patients in the initial CZP arms in comparison to controls; in pooled data in RAPID 1 the change in score from baseline to week 16 amongst ACR nonresponders was 0.2 in the CZP groups compared with 0.9 in controls ($p < 0.05$) [8]. This implies that inhibition of joint damage with CZP occurs even in poor clinical responders as has been demonstrated with other TNFi [21,22].

Patient-reported outcomes

Improvement in patient-reported outcomes has been demonstrated in patients treated with CZP in combination with MTX, and also with CZP monotherapy. *Post-hoc* analyses of Phase III trials previously discussed demonstrated that improvements can be seen as early as week 1 and are sustained through to study completion [23]; results at the completion of RAPID 1 and FAST4WARD are tabulated (Table 3). The results for RAPID 2 are similar at week 24 and therefore are not shown. Furthermore work productivity (inside and outside the home) has been assessed using the RA-specific Work Productivity Survey (RA-WPS); over 1 year of the RAPID 1 trial, CZP therapy (200 mg every 2 weeks) resulted in fewer full days of work missed in comparison to placebo in those employed (and fewer full days of housework missed), and fewer days of reduced productivity (productivity reduced by ≥50%) [24]. Analyses of patient-reported outcomes in RAPID 1 and 2 show that the improvement in physical function, pain and fatigue at week 12 (determined by achievement of at least the minimal clinical important difference) is associated with increased work productivity (inside and outside the home) at this time point [25], as well as agreement between patient-reported outcomes and objective clinical responses (ACR20 and DAS28 response) [23].

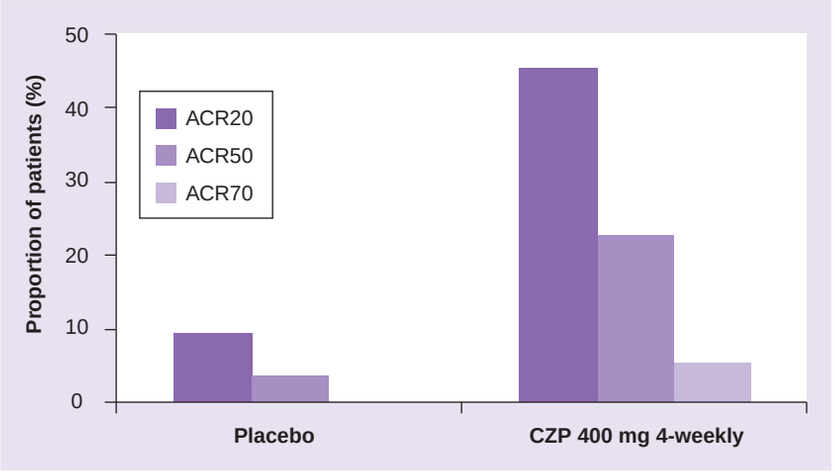

Figure 3. Proportion of patients achieving levels of response defined by the American College of Rheumatology (ACR20, ACR50 and ACR70) with certolizumab pegol monotherapy at week 24.
ACR: American College of Rheumatology; CZP: Certolizumab pegol.
Reproduced with permission from [10] © BMJ Publishing Group Ltd.

Tolerability & safety

Evidence of the safety of CZP is available from the randomized controlled trials discussed above, their open-label extension studies, as well as Phase I and II trials. Adverse event rates have been pooled from these studies, providing data from 2367 patients receiving at least one dose of CZP [26]. Its safety profile appears similar to that of other TNFi agents; however, it is important to note that trials of this nature are not powered to detect rare events such as malignancy and may exclude patients with comorbidities. Hence, safety results may not be directly applicable to the general RA population. Being relatively recently approved for clinical use, long-term observational data, such as that available for the previously established TNFi agents (etanercept, infliximab and adalimumab), is very limited.

Tolerability

In the controlled phase of the RAPID studies, adverse event rates with CZP and MTX combination therapy were similar to those receiving MTX alone [27]. In FAST4WARD, adverse events with CZP monotherapy were more

Table 3. The proportion of patients achieving clinically meaningful improvements in patient-reported outcome measures at the study end points (week 52 in RAPID 1 and week 24 in FAST4WARD).

Patient-reported outcome measure	MCID†	Patients achieving MCID or greater (%)			
		RAPID 1 [23]		*FAST4WARD* [10]	
		MTX + placebo	*MTX + CZP 200 mg 2-weekly*	*Placebo*	*CZP 400 mg 4-weekly*
HRQoL (SF-36)					
– PCS	2.5	12	42*	16	46*
– MCS	2.5	10	39*	7	34*
Physical Function (HAQ-DI)	0.22	13	47*	12	49*
Fatigue (FAS)‡	1	13	49*	17	46*
Pain (VAS)	10	14	52*	17	47*

**p < 0.001 for comparisons between active treatment and placebo groups.*
†The MCID is the minimum change from baseline considered a clinically meaningful improvement.
‡For the FAS, patients were asked to rate their tiredness on a scale of 1–10 (0 = 'no fatigue', 10 = 'fatigue as bad as you can imagine').
CZP: Certolizumab pegol; FAS: Fatigue Assessment Scale; HAQ-DI: Health Assessment Questionnaire Disability Index; HRQoL: Health-related quality of life; MCID: Minimal clinically important difference; MTX: Methotrexate; PCS: Physical component summary; SF-36: Short Form 36; VAS: Visual Analog Scale.

commonly seen than with placebo (occurring in 76% of patients compared with 58% of controls) [10]. Pooled data (including the open-label extensions of these trials) reveals adverse events in 86% of cases; most events being well tolerated, leading to withdrawal in 12% of cases out of a total exposure of 4065 patient-years in 2367 patients [26]. The most common adverse event, infection, occurred in 61% of patients.

A recent Cochrane review compared adverse events between biologic therapies, including comparison amongst the five currently available TNFi therapies [28]. Randomized controlled trials (total number 163) and open-label studies (total number 46) were included, predominantly in patients with RA, but also in patients with inflammatory bowel disease, psoriasis, psoriatic arthritis and ankylosing spondylitis. In the case of CZP, FAST4WARD and RAPID trials were included as well as three trials of CZP in Crohn's disease. The authors found that all biologics were associated with significantly higher rates of total adverse events and withdrawals in comparison to controls. Indirect comparisons revealed certolizumab did not significantly differ from other TNFi agents in rate of total adverse events or rate of withdrawal due to adverse events.

Injection-site reactions

Certolizumab pegol is associated with a low incidence of injection-site reactions, which may distinguish this agent from other TNFi therapies: a rate of less than three cases per 100 patient-years was calculated in RAPID 1 and 2 [27], and in FAST4WARD the rate reported was 5% (compared with 14% in controls) [10]. For comparison, injection-site reactions were significantly higher with adalimumab compared with placebo in the STAR study (20 vs 12%) [29]. It has been postulated that injection-site reactions and pain may be related to the local release of inflammatory mediators. *In vitro* studies have demonstrated that the PEG moiety of CZP inhibits mast cell degranulation at concentrations that might be expected at injection sites *in vivo* [30]. Moreover, research comparing *in vitro* activity of CZP amongst other TNFi therapies has shown that CZP is most potent at suppressing IL-1β and unlike other agents, does not induce apoptosis of activated peripheral blood monocytes and lymphocytes or necrosis of neutrophils [31].

Serious infection

There is an increased risk of infection with TNFi therapy, and it is contraindicated in the presence of active severe infection. Adverse events in RAPID 1 and 2 revealed rates of infection were not increased with CZP and MTX combination therapy compared with MTX controls; however, the rate of serious infection (infection requiring intravenous antibiotics, or leading to hospitalization or death) differed significantly, occurring at a rate of six per 100 patient-years (with CZP 200 mg, the dose used in clinical practice) in comparison to 1.5 per 100 patient-years in MTX controls [27]. In FAST4WARD, two patients experienced serious infection (1.8%) with CZP monotherapy, whereas no incidences were observed in controls [10]. In the more recent study, REALISTIC, the incidence

of serious infections was similar between CZP and controls (2.6 vs 1.9%) [19].

In a Cochrane review, discussed previously, comparing adverse events between biologic therapies (see 'Tolerability & safety' section above), CZP was associated with significantly higher odds of serious infection compared with etanercept, infliximab, adalimumab and golimumab [28]. However, the heterogeneity of included studies must be borne in mind. In particular, in two of the RA studies included in this review (RAPID 2 and FAST4WARD) there were no serious infections observed in control arms; in part, at least, this may be explained by the design of these studies in which patients were withdrawn (for ethical reasons) if not clinically responding (84 and 69% were withdrawn in control arms in RAPID 2 and FAST4WARD, respectively). This causes difficulty in assessing the relative risk of serious infection associated with CZP. Across the clinical studies, incidence of serious infections in patients receiving CZP is comparable with other TNFi agents, and the rates of serious infection with CZP in trials is comparable to observational data for other TNFi agents: pooled data from the British biologics registry (BSRBR) is available for patients receiving infliximab, etanercept or adalimumab, which indicates a rate of six serious infections per 100 patient-years (patients receiving CZP only recently been added to the registry in 2010) [32].

Tuberculosis

The most common serious infections seen in studies of CZP were respiratory tract infections (1.3 incidences per 100 patient-years) and tuberculosis (0.7 incidences per 100 patient-years) [26]. The risk of tuberculosis (either reactivation of latent infection or increased susceptibility to infection) is increased with all TNFi therapies; in particular, higher incidences are associated with the use of the monoclonal antibodies (infliximab and adalimumab) in comparison to the TNF receptor fusion protein etanercept [33]. All patients should be screened for latent tuberculosis infection prior to receiving TNFi. The risk depends partly on the background prevalence of tuberculosis: most cases in studies of CZP occurred in countries with high prevalence for the disease, with no incidences seen, for instance, in the USA [26]. Of note is that these study protocols allowed inclusion of patients with a positive skin test (purified protein derivative test ≥5 mm), with normal chest x-ray and no clinical signs of tuberculosis, at the discretion of the physician.

Opportunistic infection

Cases of fungal infections with TNFi, for example histoplasmosis or aspergillosis, have been reported, although the incidence is extremely low [34]. In patients receiving CZP in the aforementioned studies there were five cases of fungal infection out of a total exposure of 4065 patient-years: three cases of fungal esophagitis, one case of geotrichosis and one case of pneumocystosis [26].

Malignancy

A history of malignancy, and in particular lymphoproliferative malignancy, is a relative contraindication to TNFi. Difficulties arise in establishing the risk with TNFi as rates of malignancy, in particular lymphoma, are increased in RA. Increased rates observed from patient registries may reflect higher levels of disease activity in these patients who have required TNFi therapy. In CZP studies, standardized incidence ratios were 1.2 (95% CI: 0.8–1.2) for malignancy and 4.1 (95% CI: 0.8–12.0) for lymphoma [26]. Data from a French registry (RATIO) demonstrate a similar standardized incidence ratios for Hodgkin's lymphoma in patients receiving etanercept, infliximab or adalimumab: 5.05 (95% CI: 2.41–10.60) [35].

Conclusion

The evidence summarized above indicates CZP is effective and well-tolerated in its licensed indication (DMARD-resistant RA) at its recommended dose (400 mg at weeks 0, 2 and 4, followed by 200 mg every 2 weeks for maintenance) in combination with MTX or as a monotherapy. Combination with MTX therapy is preferable if tolerated; randomized controlled trials of other TNFi agents, with monotherapy and combination therapy arms, demonstrate superior clinical and structural outcomes associated with concomitant MTX. In addition, antibody formation against TNFi, a proposed mechanism for nonresponse to biologic therapies, is reduced by concomitant MTX; this includes data available for CZP [101]. Comparison between CZP combination therapy and CZP monotherapy is problematic as baseline characteristics of patients studied in the studies varied (Table 1). The REALISTIC study allows some comparison between efficacy of monotherapy and combination therapy, suggesting ACR20 responses are not markedly different [18,19].

Although lower trough concentrations in the plasma are attained with 4-weekly dosing [36], efficacy data from FAST4WARD

support maintenance dosing at 400 mg every 4 weeks. This maintenance regimen is currently recognized by US and Canadian authorization bodies, but not in Europe.

Care needs to be exercised in extrapolating response rates to predict response in clinical practice. High baseline disease activity in these clinical trials of CZP may not be relevant to the general RA population (average DAS28 ranged between 6.3 and 7 in trials summarized in TABLE 1); potential response (measured by improvement criteria) in patients with less active disease may be diminished, although REALISTIC (mean baseline DAS28 score was 5.7) and CERTAIN trials provide some insight. Previous exposure to DMARDs may also be lower than that observed in a clinical setting, ranging from 1.2 to 2 in the three trials (excluding MTX). Furthermore, although comparable to previous trials of TNFi agents, the mean dose of MTX at baseline was somewhat lower compared with what may be considered standard in current clinical practice: mean MTX dose in groups across the RAPID 1 and RAPID 2 trials was 12.2–13.6 mg.

The efficacy of CZP has been assessed in patients with an inadequate response to conventional DMARD therapy, hence it being licensed for use in this patient group. However, other TNFi agents have been trialed in patients with earlier disease, prior to the failure of MTX and/or other DMARDs, with promising results; it is yet to be established whether CZP demonstrates efficacy in this patient group in which active comparators such as MTX may achieve good responses. RAPID 1 and FAST4WARD did not address the issue of previous biologic use at baseline and in RAPID 2 there were only two patients who had previous exposure to alternative TNFi therapies. The REALISTIC study, however, suggests CZP is effective despite previous TNFi failure [19]. Further data are needed to establish how CZP performs outside the controlled trial environment, in early disease and in patients previously failing alternative non-TNFi therapies.

Discussion

Clinical use of CZP: are there any advantages of CZP over other TNFi?

Certolizumab pegol is positioned for use in RA patients for whom DMARD therapy is inadequate. A number of other biologic therapies are also licensed for use in this circumstance: the four alternative TNFi therapies and abatacept (with tocilizumab also licensed for this indication in Europe). In the first trial directly comparing efficacy of these therapeutic options, abatacept demonstrated similar clinical efficacy to infliximab in MTX inadequate responders [37]; however, there are a paucity of such head-to-head trials. Plans for a trial directly comparing two TNFi therapies (certolizumab and adalimumab), the first of its kind, have recently been announced [102]. Comparison across randomized controlled trials has been undertaken using the number needed to treat (NNT) to achieve response, as this should not be affected by clinical differences between the study populations, without revealing any remarkable differences; amongst new biologic therapies (including CZP), the NNT to achieve one ACR50 response at 1 year was between 4 and 6 [38], and amongst all five available TNFi therapies, the NNT for ACR50 response at 6 months fell between 3 and 5 [39]. Use of a loading regimen with CZP may improve its speed of onset; a pharmacokinetic study demonstrated that 80% of ultimate ACR20 responders achieved this response at week 8, compared with week 12 when loading was not undertaken [40], and in the RAPID Phase III trials (in which a loading regimen was employed) continued improvements in ACR20 response were seen up to week 12, after which they plateaued [8,9]. This onset of action appears similar to other subcutaneously administered TNFi such as adalimumab [3], whilst with intravenous infliximab response may be more rapid (in the ATTRACT study, 90% of the total number of ACR20 responders achieved this response by week 6) [2].

Whilst no notable differences in efficacy have been elucidated to date, a range of TNFi agents differing in their method of administration allows treatment to be tailored to an individual patient's preference. The unique structure of CZP may also confer subtle advantages over other TNFi, perhaps prompting its use on an individual patient basis. That its component fragment of monoclonal antibody is humanized, and that it is without the constant fragment of immunoglobulin (Fc), may bestow a reduced risk of immunogenicity, possibly contributing to the lower rate of injection-site reactions observed in trials. Lack of the Fc component may also be relevant to use in females of reproductive age, with the suggestion that CZP may be less likely to cross the placenta, as discussed above [13,14].

One limitation to the use of biologic therapies is financial cost. Economic evaluations have generally shown TNFi to be cost effective across multiple healthcare settings for patients

in whom conventional DMARD therapy has failed, in comparison to continuing management with these standard DMARD therapies [41–43]. With a structure distinct from alternative TNFi (with one antibody fragment per molecule), the prospect of reduced manufacturing costs of CZP has not materialized [44]. There may be financial advantages to choosing CZP in certain locations; for example in the UK, the Patient Access Scheme allows provision of the first ten doses of CZP therapy at no cost to the National Health Service [45]. Cost–effectiveness analyses in the UK, incorporating this scheme, demonstrate CZP is cost effective as a monotherapy and in combination with MTX. At the willingness-to-pay threshold of £20,000 per quality adjusted life-year gained, probabilistic sensitivity analyses have demonstrated the probability of CZP being cost effective to be approximately 50% (reported as 53.6 [46] and 48.7% [45] when used in combination with MTX and 46.2% when used as monotherapy [45]). Ability to compare TNFi agents is limited by the lack of head-to-head studies and the variation in incremental cost–effectiveness ratios between studies. *Post-hoc* analysis of Phase III studies have shown that 12 weeks (ten doses) of CZP is an adequate period to determine whether response will be achieved, with response at 12 weeks predictive of good clinical and radiographic outcomes at 1 year [16,47].

Future perspective

One potential consequence of the introduction of additional new TNFi therapies may be that, with increased competition amongst TNFi, the price of these products will be driven down. Increased cost–effectiveness may favor their use, encourage switching between TNFi in the event of initial TNFi failure or enable use in circumstances where availability may have previously been restricted, for example restraints imposed by medical insurers or in state-funded healthcare systems (e.g., the UK where a criterion of high disease activity must be met).

Although not available for CZP, there is evidence to suggest that the response to TNFi is superior in early disease, prior to the failure of conventional DMARDs. Higher rates of remission have been achieved [48], and sustained remission despite withdrawal of TNFi therapy is more readily achievable [49,50]. Evidence supporting the early use of TNFi, before the failure of conventional DMARDs, is increasing such that recent recommendations by the European League Against Rheumatism (EULAR) suggest the use of TNFi therapy in combination with MTX as first-line therapy in patients with poor prognostic signs for rapidly progressive disease, such as early radiographic damage or very high disease activity [51]. Cost–effectiveness of first-line TNFi therapy for RA remains controversial [52]; economic models simplify a complex situation of long-term medical expenses (which often rise with increasing disease duration), societal costs (including the costs of informal care) and reduced productivity, which remain difficult to quantify from short-term studies.

The recent addition of CZP, along with other new biologic therapies that have recently been introduced, highlights the pressing need for the development of biomarkers that could potentially predict response to therapy, therefore aiding physicians' decisions regarding choice of biologic. The ability to shorten the time to effectively control disease would be invaluable in the management of RA patients in the future.

Financial & competing interests disclosure

P Emery has provided expert advice and undertaken clinical trials for Pfizer, Merck, Abbott, UCB, BMS and Roche. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

Executive summary

- Certolizumab pegol in combination with methotrexate or as a monotherapy improves clinical and functional outcomes in patients with active rheumatoid arthritis with an inadequate response to disease-modifying antirheumatic drug therapy, and is licensed for use in these patients in the USA, Canada and Europe.
- Certolizumab pegol in combination with methotrexate improves radiographic outcomes in patients with active rheumatoid arthritis.
- Safety data in clinical trials indicate the incidence of injection-site reactions and injection-site pain is less with certolizumab pegol compared with other subcutaneous TNF inhibitor therapies (etanercept and adalimumab). Safety outcomes in the long term are yet to be fully established. *In vitro* evidence suggests certolizumab pegol may be less likely to cross the placenta than other TNF inhibitor therapies, however, further data are needed to determine safety of exposure during pregnancy.
- The dose of certolizumab pegol recommended for use in clinical practice (based on current data) is 200 mg every 2 weeks after initial loading (400 mg at weeks 0, 2 and 4). Maintenance dosing at 400 mg every 4 weeks is also approved in the USA and Canada.

Bibliography

Papers of special note have been highlighted as:
- ▪ of interest
- ▪▪ of considerable interest

1 Weinblatt ME, Kremer JM, Bankhurst AD *et al.* A trial of etanercept, a recombinant tumor necrosis factor receptor:Fc fusion protein, in patients with rheumatoid arthritis receiving methotrexate. *N. Engl. J. Med.* 340(4), 253–259 (1999).

2 Maini R, St Clair EW, Breedveld F *et al.* Infliximab (chimeric anti-tumour necrosis factor α monoclonal antibody) versus placebo in rheumatoid arthritis patients receiving concomitant methotrexate: a randomised Phase III trial. *Lancet* 354(9194), 1932–1939 (1999).

3 Weinblatt ME, Keystone EC, Furst DE *et al.* Adalimumab, a fully human anti-tumor necrosis factor α monoclonal antibody, for the treatment of rheumatoid arthritis in patients taking concomitant methotrexate: the ARMADA trial. *Arthritis Rheum.* 48(1), 35–45 (2003).

4 Buch MH, Bingham SJ, Bryer D, Emery P. Long-term infliximab treatment in rheumatoid arthritis: subsequent outcome of initial responders. *Rheumatology* 46(7), 1153–1156 (2007).

5 Buch MH, Vital EM, Dass S, Das S, Bryer D, Emery P. Switching to rituximab and an alternative tnf inhibitor in patients with rheumatoid arthritis that have failed previous TNF inhibitor are both effective treatment options with good maintenance rates (abstract). *Ann. Rheum. Dis.* 69(Suppl. 3), 379 (2010).

6 Smolen JS, Kay J, Doyle MK *et al.* Golimumab in patients with active rheumatoid arthritis after treatment with tumour necrosis factor α inhibitors (GO-AFTER study): a multicentre, randomised, double-blind, placebo-controlled, Phase III trial. *Lancet* 374(9685), 210–221 (2009).

7 Buch MH, Conaghan PG, Quinn MA, Bingham SJ, Veale D, Emery P. True infliximab resistance in rheumatoid arthritis: a role for lymphotoxin α? *Ann. Rheum. Dis.* 63(10), 1344–1346 (2004).

8 Keystone E, Heijde DVD, Mason D *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.* 58(11), 3319–3329 (2008).

▪▪ **Phase III trial demonstrating the clinical efficacy of certolizumab pegol (CZP) in combination with methotrexate (MTX) in rheumatoid arthritis (RA). Radiographic outcomes were assessed, demonstrating decreased progression of structural joint damage with CZP in combination with MTX.**

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.* 68(6), 797–804 (2009).

▪▪ **Phase III trial demonstrating the clinical efficacy of CZP in combination with MTX in RA. Radiographic outcomes were assessed, demonstrating decreased progression of structural joint damage with CZP in combination with MTX.**

10 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.* 68(6), 805–811 (2009).

▪▪ **Phase III trial demonstrating the clinical efficacy of CZP as a monotherapy in RA. 4-weekly administration was assessed in comparison to 2-weekly administration assessed in other Phase III trials.**

11 Nesbitt A, Fossati G, Bergin M *et al.* Mechanism of action of certolizumab pegol (CDP870): *in vitro* comparison with other anti-tumor necrosis factor α agents. *Inflamm. Bowel Dis.* 13(11), 1323–1332 (2007).

12 Palframan R, Airey M, Moore A, Vugler A, Nesbitt A. Use of biofluorescence imaging to compare the distribution of certolizumab pegol, adalimumab, and infliximab in the inflamed paws of mice with collagen-induced arthritis. *J. Immunol. Methods* 348, 36–41 (2009).

13 Porter C, Kopotsha T, Smith B, Nesbitt A, Urbaniak S, Armstrong-Fisher S. No significant transfer of certolizumab pegol compared with IgG in the perfused human placenta *in vitro* (abstract). *Ann. Rheum. Dis.* 69(Suppl. 3), 210 (2010).

14 Wolf D, Mahadevan U. Certolizumab pegol use in pregnancy: low levels detected in cord blood (abstract). *Arthritis Rheum.* 62(Suppl. 10), 299 (2010).

15 Van Vollenhoven RF, Felson D, Strand V, Weinblatt ME, Luijtens K, Keystone EC. American College of Rheumatology hybrid analysis of certolizumab pegol plus methotrexate in patients with active rheumatoid arthritis: data from a 52-week Phase III trial. *Arthritis Care Res.* 63(1), 128–134 (2011).

16 Van Der Heijde D, Schiff M, Keystone E *et al.* Time to and level of initial DAS28 change with certolizumab pegol predicts the likelihood of having low disease activity at years 1 and 2 in patients with rheumatoid arthritis (abstract). *Ann. Rheum. Dis.* 69(Suppl. 3), 505 (2010).

17 Smolen JS, Van Vollenhoven RF, Kavanaugh A *et al.* Efficacy and safety of certolizumab pegol plus methotrexate in patients with rheumatoid arthritis (RA): 3-year data from the RAPID 2 study. *Arthritis Rheum.* 62, 1806 (2010).

18 Weinblatt M, Fleischmann R, Emery P *et al.* Efficacy and safety of certolizumab pegol in a clinically representative population of patients (pts) with active rheumatoid arthritis (RA): results of the REALISTIC Phase IIIb randomized controlled study. *Arthritis Rheum.* 62, 1805 (2010).

19 Weinblatt M, Fleischmann R, Van Vollenhoven RF *et al.* Certolizumab pegol as monotherapy or with concomitant DMARDS in patients with active rheumatoid arthritis (RA) with or without prior TNF inhibitor use: analyses of the REALISTIC 12-week Phase IIIB randomised controlled study (abstract). *Ann. Rheum. Dis.* 70(Suppl. 3), 414 (2011).

20 Smolen JS, Emery P, Ferraccioli G *et al.* Efficacy and safety of certolizumab pegol after incomplete response to DMARDS in RA patients with low to moderate disease activity: results from CERTAIN, a phase IIIB study (abstract). *Ann. Rheum. Dis.* 70(Suppl. 3), 259 (2011).

21 Emery P, Genovese MC, Van Vollenhoven R, Sharp JT, Patra K, Sasso EH. Less radiographic progression with adalimumab plus methotrexate versus methotrexate monotherapy across the spectrum of clinical response in early rheumatoid arthritis. *J. Rheumatol.* 36(7), 1429–1441 (2009).

22 Lipsky PE, Van Der Heijde DM, St Clair EW *et al.* Infliximab and methotrexate in the treatment of rheumatoid arthritis. *N. Engl. J. Med.* 343(22), 1594–1602 (2000).

23 Strand V, Mease P, Burmester G *et al.* Rapid and sustained improvements in health-related quality of life, fatigue, and other patient-reported outcomes in rheumatoid arthritis patients treated with certolizumab pegol plus methotrexate over 1 year: results from the RAPID 1 randomized controlled trial. *Arthritis Res. Ther.* 11(6), R170 (2009).

24 Kavanaugh A, Smolen JS, Emery P *et al.* Effect of certolizumab pegol with methotrexate on home and work place productivity and social activities in patients with active rheumatoid arthritis. *Arthritis Care Res.* 61(11), 1592–1600 (2009).

25 Hazes JM, Taylor P, Strand V, Purcaru O, Coteur G, Mease P. Physical function improvements and relief from fatigue and pain are associated with increased productivity at work and at home in rheumatoid arthritis patients treated with certolizumab pegol. *Rheumatology* 49(10), 1900–1910 (2010).

26 Van Vollenhoven RF, Smolen JS, Schiff M *et al.* Safety Update on certolizumab pegol in patients with active rheumatoid arthritis (abstract). *Arthritis Rheum.* 60(Suppl. 10), 1699 (2009).

▪ **Adverse event data for patients receiving CZP in RA clinical trials and open-label extensions have been pooled in this analysis to provide the overall incidence of adverse events (per 100 patient-years) and standardized incidence ratios for malignancies, up to 2007.**

27 Mease PJ. Certolizumab pegol in the treatment of rheumatoid arthritis: a comprehensive review of its clinical efficacy and safety. *Rheumatology* 50(2), 261–270 (2011).

28 Singh JA, Wells GA, Christensen R *et al.* Adverse effects of biologics: a network meta-analysis and Cochrane overview. *Cochrane Database Syst. Rev.* 2, CD008794 (2011).

29 Furst DE, Schiff MH, Fleischmann RM *et al.* Adalimumab, a fully human anti tumor necrosis factor-α 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.* 30(12), 2563–2571 (2003).

30 Lamour S, Bracher M, Nesbitt A. The PEG component of certolizumab pegol inhibits degranulation by stimulated mast cells (abstract). *Arthritis Rheum.* 60(Suppl. 10), 44 (2009).

31 Fossati G, Nesbitt A. Certolizumab pegol has a different profile from the other anti-TNFs, including golimumab, in a variety of *in vitro* assays (abstract). *Ann. Rheum. Dis.* 69(Suppl. 3), 324 (2010).

▪▪ **The following were assessed, *in vitro*, for all commercially available TNF inhibitor agents, in respect to their mechanism of action: ability to neutralize TNF, ability to inhibit activation of monocytes, ability to induce apoptosis of peripheral blood lymphocytes and effect on neutrophil necrosis. Differences between CZP and other TNF inhibitors were demonstrated.**

32 Dixon WG, Symmons DPM, Lunt M, Watson KD, Hyrich KL, Silman AJ. Serious infection following anti-tumor necrosis factor α therapy in patients with rheumatoid arthritis: lessons from interpreting data from observational studies. *Arthritis Rheum.* 56(9), 2896–2904 (2007).

33 Dixon WG, Hyrich KL, Watson KD *et al.* Drug-specific risk of tuberculosis in patients with rheumatoid arthritis treated with anti-TNF therapy: results from the British Society for Rheumatology Biologics Register (BSRBR). *Ann. Rheum. Dis.* 69(3), 522–528 (2010).

34 Desai SB, Furst DE. Problems encountered during anti-tumour necrosis factor therapy. *Best Pract. Res. Clin. Rheumatol.* 20(4), 757–790 (2006).

35 Mariette X, Tubach F, Ravaud P *et al.* Patients on anti-TNF have an increased risk of lymphoma compared with the general population. Results of the French RATIO observatory. *Ann. Rheum. Dis.* 67(Suppl. 2), 323 (2008).

36 Lacroix BD, Parker GL. Dosing with certolizumab pegol (CZP) 200 mg every 2 weeks (Q2w) provides higher plasma trough concentrations than 400 mg every 4 weeks (Q4w). *Gastroenterology* 138(Supp. 1), S163–S164 (2010).

37 Schiff M, Keiserman M, Codding C *et al.* Efficacy and safety of abatacept or infliximab vs placebo in ATTEST: a Phase III, multi-centre, randomised, double-blind, placebo-controlled study in patients with rheumatoid arthritis and an inadequate response to methotrexate. *Ann. Rheum. Dis.* 67(8), 1096–1103 (2008).

38 Kristensen L, Jakobsen A, Bartels E *et al.* The number needed to treat for second-generation biologics when treating established rheumatoid arthritis: a systematic quantitative review of randomized controlled trials. *Scand. J. Rheumatol.* 40(1), 1–7 (2011).

39 Scott DL, Cope A. New tumour necrosis factor inhibitors for rheumatoid arthritis: are there benefits from extending choice? *Ann. Rheum. Dis.* 68(6), 767–769 (2009).

40 Lacroix BD, Lovern MR, Stockis A, Sargentini-Maier ML, Karlsson MO, Friberg LE. A pharmacodynamic markov mixed-effects model for determining the effect of exposure to certolizumab pegol on the ACR20 score in patients with rheumatoid arthritis. *Clin. Pharmacol. Ther.* 86(4), 387–395 (2009).

41 Brennan A, Bansback N, Nixon R *et al.* Modelling the cost effectiveness of TNF-α antagonists in the management of rheumatoid arthritis: results from the British Society for Rheumatology Biologics Registry. *Rheumatology* 46(8), 1345–1354 (2007).

42 Tanno M, Nakamura I, Ito K *et al.* Modeling and cost–effectiveness analysis of etanercept in adults with rheumatoid arthritis in Japan: a preliminary analysis. *Mod. Rheumatol.* 16(2), 77–84 (2006).

43 Bansback NJ, Brennan A, Ghatnekar O. Cost effectiveness of adalimumab in the treatment of patients with moderate to severe rheumatoid arthritis in Sweden. *Ann. Rheum. Dis.* 64(7), 995–1002 (2005).

44 Barnes T, Moots R. Targeting nanomedicines in the treatment of rheumatoid arthritis: focus on certolizumab pegol. *Int. J. Nanomedicine* 2(1), 3–7 (2007).

45 National Institute for Health and Clinical Excellence. Certolizumab Pegol for the treatment of rheuamtoid arthritis. TA186. *London: National Institute for Health and Clinical Excellence* (2010).

46 Purcaru O, Taylor P, Emery P, Palmer S. Cost–effectiveness of certolizumab pegol plus methotrexate or as monotherapy for the treatment of active rheumatoid arthritis in the United Kingdom (abstract). *Ann. Rheum. Dis.* 69(Suppl. 3), 718 (2010).

47 Keystone EC, Curtis JR, Fleischmann RM *et al.* Rapid improvement in the signs and symptoms of rheumatoid arthritis following certolizumab pegol treatment predicts better longterm outcomes: *post-hoc* analysis of a randomized controlled trial. *J. Rheumatol.* 38(6), 990–996 (2011).

48 Emery P, Kvein TK, Combe B *et al.* Very early (<4 months) treatment with combination etanercept and methotrexate produces significantly better remission rates: results from the COMET study. *Ann. Rheum. Dis.* 69(Suppl. 3), 57 (2010).

49 Bejarano V, Conaghan PG, Quinn MA, Saleem B, Emery P. Benefits 8 years after a remission induction regime with an infliximab and methotrexate combination in early rheumatoid arthritis. *Rheumatology* 49(10), 1971–1974 (2010).

50 Saleem B, Keen H, Goeb V *et al.* Patients with RA in remission on TNF blockers: when and in whom can TNF blocker therapy be stopped? *Ann. Rheum. Dis.* 69(9), 1636–1642 (2010).

51 Smolen JS, Landewé R, Breedveld FC *et al.* EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs. *Ann. Rheum. Dis.* 69(6), 964–975 (2010).

52 Finckh A, Bansback N, Marra CA *et al.* Treatment of very early rheumatoid arthritis with symptomatic therapy, disease-modifying antirheumatic drugs, or biologic agents: a cost–effectiveness analysis. *Ann. Intern. Med.* 151(9), 612–621 (2009).

Websites

101 EMEA/H/C/001037 -II/0009 – Cimzia: European Public Assessment Report, Summary of Product Characteristics. *European Medicines Agency* January 2010 (updated February 2011) www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/001037/WC500069763.pdf (Accessed February 2011)

102 UCB Press Release. UCB to conduct first anti-TNF head-to-head study between Cimzia® (certolizumab pegol) and Humira® (adalimumab) Brussels, 25 May 2011 www.ucb.presscentre.com/content/detail.aspx?ReleaseID=494&NewsAreaID=2&changeCurrentLocale=1