Review

Certolizumab for rheumatoid arthritis

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ABSTRACT

This is a review of the pharmacology of certolizumab pegol and its efficacy and safety in the treatment of patients with rheumatoid arthritis refractory to synthetic disease-modifying anti-rheumatic drugs (DMARDs). Certolizumab is a new anti-TNF-α biologic agent injected subcutaneously with an innovative molecular structure and unique pharmacodynamic and pharmacokinetic properties. Data from controlled clinical trials indicate that the drug is effective in reducing disease activity and disability. It also inhibits radiographic progression. Certolizumab administration has an acceptable safety profile. The clinical data available suggest that the nature of adverse events is generally comparable to that of other TNF-α blockers. Given its rapid onset of action certolizumab presents an attractive alternative therapeutic option for patients with moderate to severe RA refractory to DMARDs.

Introduction

Rheumatoid arthritis (RA) is an autoimmune inflammatory disease that affects a significant proportion of the population. Epidemiological studies carried out in European and North American areas estimate a prevalence of 0.5-1%, and a mean annual incidence of 0.02–0.05% (1-3). RA is related to an increased mortality and the survival of RA patients is estimated to be shortened by 4–10 years (4).

Unless treated early and effectively, the disease may severely affect the patients' quality of life being a source of chronic pain, fatigue, loss of function, permanent disability and loss of productivity. The disease impairs several aspects of personal and social life, including mood and emotions, mental health, vitality, participation in everyday tasks and hobbies, as well as relationship with others (5). All these not only have a significant impact on a personal level, but also confer a significant economic burden to the society.

Newly licensed medications, especially biological agents, have enabled the attainment of remission in RA patients. Definite treatment targets goals, tight disease control and patient-individualised treatment approach are essential requisitions to design optimal treatment strategies in daily clinical practice (6, 7).

The role of TNF-α in RA pathogenesis

Advances in our understanding of the pathogenesis of the disease and particularly the role of cytokines have resulted in the advent of modern therapies with the use of biologic drugs. Tumor necrosis factor α (TNF-α) has been the first of a series of cytokines to be investigated in RA and further, as basic research paved the way to clinical trials, the first to serve as a therapeutic target. TNF-α is a pleiotropic cytokine involved in the inflammatory process and has been shown to be a mediator of such chronic diseases as RA, spondylarthropathies and Crohn's disease. As regards RA, the dominant pathophysiological role of TNF-α has initially been illustrated several years ago, when a transgenic (Tg) mouse model that over-expressed TNF-α also developed an erosive polyarthritis very similar to human RA (8). Since then considerable knowledge has accumulated concerning its production, regulation and effects in RA within what is now known as "the cytokine network" (9).

TNF-α is produced by monocytes and macrophages, dendritic cells, B and T cells, mast cells, osteoblasts and fibroblasts, but also by adipocytes, keratinocytes, mammary and colonic epithelial cells, as well as plenty of other cell types (10). Macrophages are the major source of TNF-α and are also highly responsive to it. TNF-α is a homotrimeric cytokine synthesised as a membrane-bound protein, which can be cleaved

by proteases to release the soluble cytokine. However, the molecule either in its transmembrane or the soluble form is biologically active.

TNF-α signals through two transmembrane receptors, the p55/TNFR1 and the p75/TNFR2 regulating an array of critical cell functions including cell proliferation, differentiation, survival, and apoptosis (11). TNFR1 (p55) and TNFR2 (p75) can be cleaved from the cell membrane and circulate in a soluble form. These soluble forms preserve the ability to bind free TNF-α and thus act as decoy receptors with the potential to play a regulatory role in a variety of processes mediated by TNF-α in health and disease (12).

Binding of TNF-α to either receptor, TNFR1 and TNFR2, results in the recruitment of signal transducers that activate at least three distinct effector pathways. Through complex signaling cascades and networks, these pathways lead to the activation of caspases and a pair of transcription factors, activation protein-1 and nuclear factor kappa B (NFκB) (13, 14).

Although the significance of TNF-α in the autoimmune diseases is well established, our knowledge regarding its receptors and their role in disease is not so clear (15). Using animal models of inflammatory arthritis, TNFR1 has been identified as a key molecule in arthritis development: TNFR1-deficient mice show reduced development of collagen-induced arthritis (CIA) (16) and in human TNF-α Tg mice lack of TNFR1 completely protects these animals from arthritis. Moreover, re-introduction of TNFR1 in mesenchymal cells is sufficient to allow for the development of full-blown TNF-α-dependent arthritis (17). Furthermore, TNFR1 mediates local bone destruction by enhancing the generation of osteoclasts (18, 19). In addition, as mentioned above, there are multiple large clinical studies demonstrating the effectiveness of TNF-α blockade in various diseases.

Anti-TNF-α blocking treatment

In the mid 80s the idea of neutralising TNF-α via a specific antibody emerged. The hypothesis was that reducing TNF-α levels would restore the balance in the cytokine system. Thus infliximab, a chimeric human-murine monoclonal antibody that binds with high affinity to both soluble and transmembrane forms of TNF-α, but not to lymphotoxin α (TNFβ), was developed with the employment of genetic engineering techniques. Infliximab inhibits the functional activity of TNF-α in a wide variety of *in vitro* assays. In transgenic mice overexpressing human TNF-α, infliximab prevented the development of polyarthritis and, when administered after disease onset, it allowed affected joints to heal. *In vivo*, infliximab rapidly forms stable complexes with human TNF-α, a process that parallels the loss of TNF-α bioactivity (101). Finally, infliximab has been successfully tried in a number of autoimmune diseases, such as RA, Crohn's disease, ulcerative colitis, ankylosing spondylitis, psoriatic arthritis and psoriasis and is officially licensed for their treatment (101). Since the advent of infliximab, four more genetically engineered molecules have been marketed, etanercept, adalimumab, golimumab and more recently certolizumab, each employing a slightly different compositional and pharmacodynamic approach.

Etanercept is a fusion protein consisting of the extracellular ligand binding domain of the human TNFR/p75 and of the constant fragment (fragment crystallisable, Fc) of the human immunoglobulin G1 (IgG_1). This Fc component contains the hinge, CH2 and CH3 regions, but not the CH1 region of IgG1 (102). Adalimumab is a recombinant human monoclonal antibody against TNF-α. It binds specifically TNF-α neutralising its biological function by blocking its interaction with the p55 and p75 cell surface TNF-α receptors (103). Golimumab is also a human IgG1-κ monoclonal antibody produced by a murine hybridoma cell line with recombinant DNA technology (104). It forms high affinity, stable complexes with both the soluble and transmembrane forms of human TNF-α preventing the binding of TNF-α to its receptors.

Certolizumab

Certolizumab pegol is a recombinant humanised antibody fragment that consists of the light and the heavy chain, linked via a disulfide bond, of the antigen-binding fragment (Fab') of an anti-TNF-α monoclonal antibody. The humanised Fab' component of the drug is of murine hybridoma origin expressed in *Escherichia coli*. After purification, the Fab' component is covalently conjugated via a maleimide group to an approximately 40kDa polyethylene glycol (PEG) in order to extend its plasma half-life. Engineering of the Fab' fragment with a single free cysteine residue in the hinge region enables site-specific attachment of PEG without affecting the ability of the Fab' fragment to bind and neutralise TNF-α (20, 21) (Fig. 1). Certolizumab does not contain a fragment crystallisable (Fc) region, which is normally present in a complete antibody, and therefore does not fix complement or cause antibody-dependent cell-mediated cytotoxicity *in vitro*. It does not induce apoptosis *in vitro* in human peripheral blood-derived monocytes or lymphocytes nor neutrophil degranulation (22).

In addition, the absence of the Fc region in certolizumab pegol does not allow for neonatal Fc receptor (FcRn)-mediated transport and recycling. This, as well as the physicochemical properties endowed by pegylation might explain the preferential distribution and retention of certolizumab in the inflamed tissues (23).

Certolizumab pegol is also distinct among anti-TNF-α monoclonal antibodies by its valency: this compound is univalent, thus reducing the potential for large immune complex formation (24), whereas infliximab, adalumimab and golimumab are divalent with the potential to form large immune complexes.

Certolizumab has a high affinity for human TNF-α and binds with a dissociation constant (KD) of 90 pM. Its epitope on TNF-α was found to be shaped by 13 aminoacids E19, A22, E23, G24, Q25, Q27, L43, R44, D45, N46, Q47, I83, R13822.This strong selective binding results in neutralisation of the TNF-α at concentrations as low as few ng/mL (IC90 of 4 ng/mL) (25). It is interesting that three of the commercially available anti-TNF-α agents, infliximab, adalimumab and etanercept, were found to

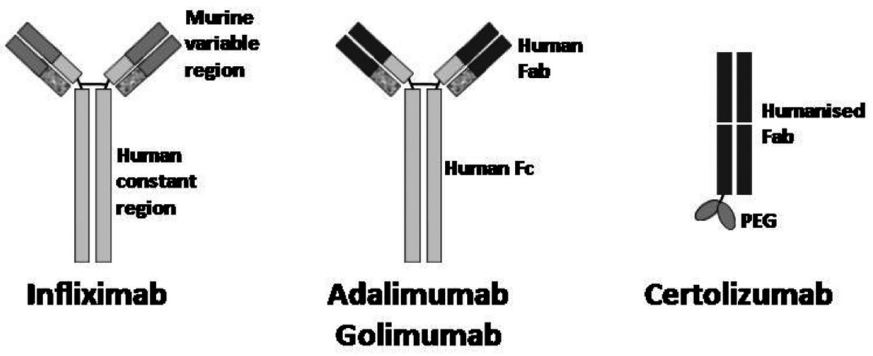

Fig. 1. Schematic representation of TNF inhibitors' structure. Etanercept is a fusion protein consisting of the extracellular ligand binding domain of the human TNFR/p75 and of the Fc (fragment crystallisable) region of the human IgG1. Infliximab is a chimeric monoclonal antibody, while adalimumab and golimumab are recombinant human monoclonal antibodies against TNF-α. Certolizumab pegol is a recombinant humanised antibody fragment that consists of the light and the heavy chain, linked via a disulfide bond, of the antigen-binding fragment (Fab') of an anti-TNF-α monoclonal antibody. The humanised Fab' component of the drug is covalently conjugated to polyethylene glycol (PEG).

bind to similar, but not identical epitopes on the TNF-α molecule. These differences in the exact epitope could explain the variations in the downstream signalling properties (26). No cross-reactivity was observed between certolizumab and native TNF-α produced in rat, guinea pig and rabbit and only weak cross-reactivity was seen with dog TNF-α (IC90 not achieved).

Moreover, certolizumab is effective in preventing TNF-α from binding to human p55 and p75 TNF-α receptors. Certolizumab is able to bind and neutralise human membrane TNF-α. Although certolizumab has a high affinity for human TNF-α, it does not neutralise lymphotoxin at concentrations up to 1 mg/mL.

Another significant differential property of certolizumab is the presence of PEG a molecule which has been widely used, in order to improve the pharmacokinetic profile and bioavailability of therapeutic proteins (27, 28). PEGylated molecules tend to diffuse slowly from blood because of the haemodynamic properties of PEG (29). This fact by itself makes certolizumab unique in terms of its distribution in inflamed and non-inflamed tissues. Indeed, the distribution of certolizumab pegol, infliximab and adalumimab has been investigated using a biofluorescence method in healthy and inflamed murine tissue in two experiments (20). All agents were conjugated with Alexa680, a low molecular weight fluorescent dye, and administered intravenously to healthy DBA/1 mice and to DBA/1 mice with collagen-induced arthritis. Levels of agents in hind paws were then measured. All three agents penetrated inflamed tissue more effectively than non-inflamed tissue, but certolizumab pegol penetrated inflamed arthritic paws most effectively and was retained for longer than infliximab or adalimumab (20).

Additionally, certolizumab may reduce accelerated atherosclerosis observed in patients with chronic inflammatory arthritis. The exact mechanisms by which TNF inhibition alters cardiovascular disease risk factors remain elusive. However, the specific effects of certolizumab on endothelial cell function have been recently investigated by Heathfield SK and colleagues (30). Certolizumab halted TNF-mediated up-regulation of the genes encoding the adhesion molecules E-selectin, VCAM-1 and ICAM-1 and it also prevented the induction of nuclear translocation of NF-κB by TNF in human aortic endothelial cells (30).

Pharmacokinetics

In order to determine the clinical pharmacology and pharmacokinetic profile of certolizumab, data derived from approximately 2000 patients with RA and healthy volunteers in several studies including dose finding studies, pharmacokinetic trials and population pharmacokinetic and/or pharmacodynamic trials have been analyzed (105). In comparison with intravenous dosing, subcutaneous certolizumab has an absolute bioavailability of ~80%. Certolizumab demonstrates linear dose-related concentrations across the dose range tested and has a mean terminal half-lifeof approximately 14 days. A population exposure-response relationship exists between average plasma concentration of certolizumab pegol during a dosing interval (Cavg) and efficacy [defined as achievement of American College of Rheumatology (ACR) 20% response criteria] (105). The typical Cavg that produces half the maximum probability of ACR 20 response was 17μg/mL (95% CI: 10-23 μg/mL).

According to a population pharmacokinetic analysis of RA patients, as regards the distribution following subcutaneous administration of certolizumab, the apparent volume of distribution (V/F) was 8.01L (105). As mentioned before certolizumab is an antibody Fab' fragment conjugated with PEG polymers. This PEGylation delays the elimination of the pegylated Fab' from the circulation by a variety of mechanisms, including decreased renal clearance, decreased proteolysis and decreased immunogenicity and thus extends the terminal plasma elimination half-life ($t_{1/2}$) of the Fab' to a value comparable with a whole antibody product (approximately 14 days for all doses tested). Clearance following subcutaneous administration of certolizumab was estimated to be 21.0 mL/h. As shown by animal models (31), after the cleavage from the Fab', the elimination of PEG polymer is performed mainly via renal excretion. It appears that the clearance of certolizumab increases approximately three times in the presence of anti-certolizumab antibodies.

Clinical efficacy of certolizumab

Dose finding studies

The clinical efficacy program of certolizumab was initiated with two Phase II trials. In the first of them (32) thirty-six patients with established RA (mean duration of 13 years) and clinically active disease were randomised in a double-blind, ascending-dose group study to a single intravenous infusion of placebo (n=12) or 1, 5 or 20 mg/kg Certolizumab (each n=8) for a time period

of 8 weeks. The patients had already received a mean of five disease-modifying anti-rheumatic drugs (DMARDs) or experimental therapies (with a 1-month washout interval before the initiation of the study). The ACR20 response rate at week 4 was 16.7%, 50%, 87.5% and 62.5% with placebo or 1, 5 and 20 mg/kg certolizumab respectively and 16.7, 25, 75 and 75% at 8 weeks. The results for ACR50 were 0, 12.5, 12.5 and 50% at 4 weeks and 0, 12.5, 12.5 and 50% (p=0.079) at 8 weeks. Certolizumab was well tolerated.

A subsequent Phase II study tested the subcutaneous administration of 50, 100 200, 400, 600 and 800mg of Certolizumab *versus* placebo for 12 weeks in 203 adult patients with established RA (mean duration >9 years) who had on average received four prior DMARDs (33). The ACR20 response rate at week 12 was 15%, 21%, 20%, 34% and 60% with placebo or 50, 100, 200 and 400 mg/kg certolizumab respectively. Similarly, ACR50 and ACR70 response were related to the dose of certolizumab administered to patients (Fig. 2). The overall results showed a superiority of the 400 mg dosage, while the higher dosages of 600 mg and 800 mg did not show any further increase in efficacy compared to 400 mg (data not shown). In this study, the most common adverse events (AEs) observed were headache, nausea and infection.

Following these two initial studies the clinical efficacy and the safety of certolizumab in RA has been assessed in 17 Phase 3 or 4 clinical trials, which have been completed, while another 25 trials are ongoing including overall 27358 patients.

Certolizumab in combination with methotrexate

A couple of pivotal studies, RAPID (Rheumatoid Arthritis Prevention of structural Damage) 1 and 2, were conducted to assess the efficacy of certolizumab in patients who had previously incomplete response to MTX (34, 35). The design of both studies was similar: multicenter, randomised prospective, double-blind, active comparator-controlled, parallel-group, in subjects with active, adult-onset RA of at least

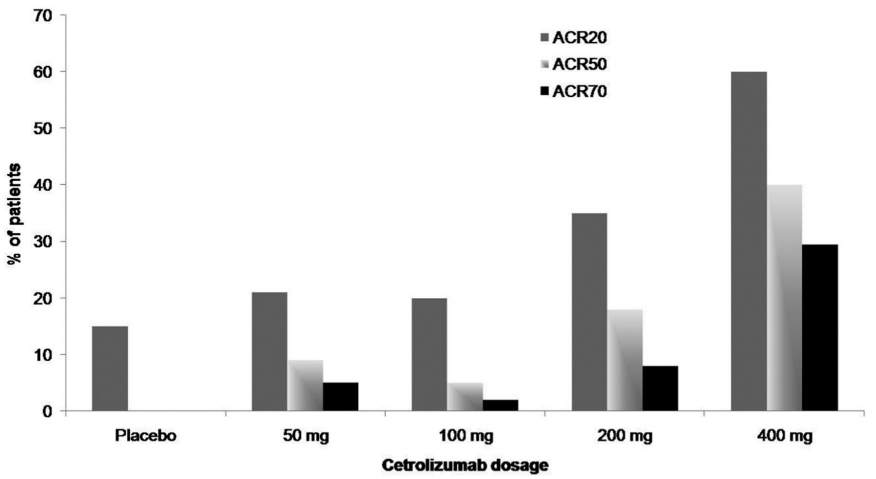

Fig. 2. The percentage of patients receiving placebo or 50, 100 200 and 400 mg of certolizumab who achieved an ACR 20%, 50% and 70% response.

6 months (but less than 15 years) duration. Participants were randomised to three non equal groups. Group 1 (40% of subjects) was treated with certolizumab 200 mg every two weeks (preceded by 3 loading doses of 400 mg each every 2 weeks), Group 2 (40% of subjects) was treated with certolizumab 400 mg every 2 weeks and finally Group 3 (20% of subjects) received placebo injections. All patients received weekly background oral MTX at a dose of at least 10 mg/week that had been stable for at least 2 months prior to study entry. The patient baseline demographics were comparable between the two RAPID trials.

The first of these trials (RAPID 1) was run for 52 weeks and had two co-primary efficacy endpoints: the proportion of patients achieving an ACR 20 response at week 24 and the change from baseline in the modified Total Sharp Score (mTSS) at week 52 (34). The results demonstrated a statistically greater efficacy of both certolizumab dosages in comparison to placebo as regards the ACR 20/50/70 response rates at week 24 as well as at week 52. More specifically, at week 24, 58.8% and 60.8% of patients treated with certolizumab 200 mg or 400 mg every two weeks with background methotrexate achieved ACR20% response criteria respectively compared to 13.6% for the placebo group (p<0.001). The respective percentages of patients achieving ACR50% and 70% response criteria were 37.1% and 21.4% (certolizumab 200 mg) and 39.9% and 20.6% (certolizumab 400 mg) (Table I). Of note, the small differences in the ACR response rates between the 2 dosages of certolizumab were neither statistically significant nor clinically meaningful. Similar results in ACR response were obtained at week 52 (Fig. 3). Moreover, the mean difference of at least 2.4 Sharp units between the certolizumab treatment groups and MTX alone group obtained over 52 weeks of therapy was also statistically significant (p<0.001) (34).

In the RAPID 2 study, with a similar design to RAPID 1, the endpoints were assessed at 24 weeks (35). The results once more showed greater efficacy of both certolizumab dosages plus MTX *versus* MTX alone ($p\leq$0.001).More specifically, 57.3%, 57.6% and 8.7% of patients receiving certolizumab 200 mg plus MTX, 400 mg plus MTX or placebo plus MTX respectively achieved an ACR20 response at 24 weeks (Table I). Certolizumab in both dose regimens plus MTX also significantly altered radiographic progression compared to MTX alone. The mean difference in modified total Sharp score (mTSS) from baseline to week 24 was at least 1.0 Sharp unit between the certolizumab treatment groups and MTX alone group ($p\leq$0.01).

Moreover, both RAPID studies have been emphasised three significant aspects of certolizumab treatment. First, certolizumab pegol with methotrex-

Table I. ACR responses (% of patients) in RA patients treated with certolizumab.

ACR response	RAPID 1 trial*,**		RAPID 2 trial^,†		REALISTIC trial*		FAST4WARD trial‡,&	
	CZP 200 mg q2w +MTX (n=393)	Placebo +MTX (n=199)	CZP 200 mg q2w +MTX (n=246)	Placebo +MTX (n=127)	CZP 200 mg q2w +DMARD (n=851)	Placebo +DMARD (n=212)	CZP 400 mg q4w monotherapy (n=111)	Placebo monotherapy (n=109)
ACR 20%								
12 weeks	67	19	62	13	51.1	25.9	48	9
24 weeks	58.8	13.6	57.3	8.7	ND	ND	45.5	9.3
52 weeks	53	13	ND	ND	ND	ND	ND	ND
ACR 50%								
12 weeks	33	7	23	4	26.6	9.9	20	0
24 weeks	37.1	7.6	32.5	3.1	ND	ND	22.7	3.7
52 weeks	37	8	ND	ND	ND	ND	ND	ND
ACR 70%								
12 weeks	16	2	9	0	12.9	2.8	5	0
24 weeks	21.4	3.0	15.9	0.8	ND	ND	5.5	0
52 weeks	22	4	ND	ND	ND	ND	ND	ND

*p<0.001. **Data at week 12 and 52 extracted from ref. 31.^p<0.001 *vs*. placebo for all comparisons except for ACR70 at week 12 (p value not significant) and for ACR70 at week 24 (p≤0.01).† Data at week 12 extracted from ref. 32. ‡p≤0.05 *vs*. placebo for all comparisons at week 12 and p<0.001 *vs*. placebo for all comparisons at week 24 except for ACR70 (p≤0.05).&Data at week 12 extracted from ref. 40.
ACR: American College of Rheumatology; CZP: certolizumab; DMARD: Disease-modifying antirheumatic drugs; FAST4WARD: eFficAcy and Safety of cerTolizumab-4 Weekly dosAge in RheumatoiD arthritis; MTX: Methotrexate; ND: Not done; q2w: every 2 weeks; q4w: every 4 weeks; RAPID: Rheumatoid Arthritis Prevention of structural Damage; REALISTIC: Certolizumab Pegol for the Treatment of Patients With Active Rheumatoid Arthritis.

ate has a fast onset of action, since the ACR20 response was already higher at week 1 than MTX alone (p<0.001). Second, the inhibition of structural damage progression was evident as early as week 12. Finally, the early response by week 12 is a good predictor of the long-term response (36).

In both RAPID studies the improvement of physical function by certolizumab was estimated using the Health Assessment Questionnaire-Disability Index (HAQ-DI) (34, 35). In RAPID 1 study, the mean change of HAQ-DI from baseline to 52 weeks was -0.60 and -0.63 in the groups of certolizumab 200 mg or 400 mg plus MTX compared to -0.18 in the group of placebo plus MTX (both comparisons were statistically significant, p<0.001). In RAPID 2 study the respective mean change of HAQ-DI from baseline to 24 weeks was-0.60 and -0.63 *versus* -0.18 (p<0.001).

In the RAPID trials as well as in their extension studies, certolizumab therapy combined to MTX has also demonstrated greater improvement in the following parameters: fatigue, health-related quality of life, home and workplace productivity and social activities compared to MTX alone (36-41). It was shown that 52.1 full days of household activities and 42.0 work days could be gained per year when patients were treated with certolizumab pegol 200 mg plus MTX rather than with MTX monotherapy (36).

In the RAPID trials, most adverse events were mild or moderate, with low incidence of withdrawals due to adverse events. However, serious infections were more common in the groups of certolizumab 200 mg (6.0 events/ 100 patient-years) or 400 mg (7.1 events/ 100 patient-years) plus MTX than in the group of placebo plus MTX (1.5 events/ 100 patient-years).

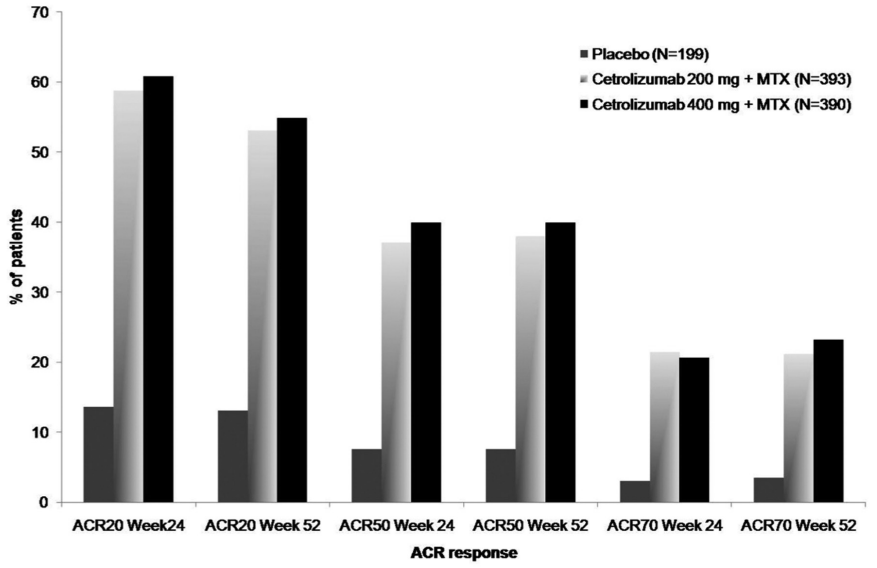

Fig. 3. ACR responses in RA patients treated with certolozumab at 24 and 52 weeks.

Certolizumab in combination with DMARDs

The Realistic study was a 12-week, double-blind, randomised, placebo controlled, phase IIIb trial of 1063 patients active RA who were inadequate responders to at least one DMARD (42). Of note, 37.6% of the 1063 patients had previous TNF inhibitor use. Patients received certolizumab (400 mg at weeks 0, 2 and 4, followed by 200 mg every

2 weeks) or placebo (every 2 weeks) plus current DMARD (MTX or other). In this study, 51.1% in the certolizumab group and 25.9% in the placebo group achieved the primary end point of ACR20 response at week 12 ($p<0.001$) (Table I). It is notable that significantly greater ACR20 and ACR50 response as well as significantly better improvement in Disease Activity Score-28 joints (erythrocyte sedimentation rate) [DAS28 (ESR)] score from baseline had already been observed in the certolizumab group at week 2. Neither the concomitant DMARD use at baseline nor the history of TNF inhibitor administration affected clinical response to certolizumab. Similarly, no differences were noted across certolizumab patient subgroups stratified by disease duration (<2 *vs*. ≥2 years).

In a subsequent study, these 1063 RA patients who had participated in the 12-week randomised double-blind REALISTIC study (42), during which they had received either certolizumab (N=851) or placebo (N=212) plus DMARD, were given the option to participate in an open-label extension (OLE) study, during which they would receive certolizumab for further 16 weeks (28 weeks in total) (106). Overall 954 patients entered the OLE study, including those 184 patients who had been previously treated with placebo. At Week 28, the efficacy results were comparable between patients who had received certolizumab for 28 weeks in total and those that had switched from placebo to certolizumab after 12 weeks. In particular, at 28 weeks, ACR20 response rates were 59.7% for patients taking certolizumab for 28 weeks and 53.3% for those on certolizumab for 16 weeks following the initial placebo phase. DAS28(C-reactive protein) [DAS28(CRP)] remission (defined as DAS28 <2.6) was achieved in 22.9% and 21.7% of patients respectively (p=not significant), while DAS28(ESR) remission (defined as DAS28(ESR) <2.6) was achieved in 15.2% and 11.4% (p=not significant) (106). In the placebo-controlled period of the trial, both adverse and serious adverse events were comparable between the two basic treatment arms. The most common adverse events were infections and infestations, musculoskeletal and connective tissue disorders, and nervous system disorders. The most common serious infections were lower respiratory tract and lung infections. The incidence of adverse events in the OLE phase was 305.8 events per 100 patient years in patients initially randomised to certolizumab in the double blind period compared to 406.2 events per 100 patient years in patients initially randomised to placebo and subsequently switched to certolizumab. The incidence of serious adverse events per 100 patient years was 14.7 *versus* 16.3, respectively.

Certolizumab as monotherapy

The 24 week FAST4WARD (eFficAcy and Safety of cerTolizumab-4 Weekly dosAge in RheumatoiD arthritis) study was designed to evaluate the efficacy of certolizumab 400 mg every 4 weeks in monotherapy. It was a randomised, double-blind, placebo-controlled trial involving patients with active, adult-onset RA of at least 6 months duration who had previously failed or were intolerant of at least one DMARD (43).

The ACR 20 response rate at week 24 was 45.5% for the treatment group which received certolizumab 400 mg compared to 9.3% for subjects who received placebo injections ($p<0.001$) (Table I) (43). Additionally, at week 24 ACR50 and ACR70 response, disease activity and patient-reported outcomes were significantly superior for certolizumab *versus* placebo. The mean change from baseline in 3-variable-DAS28(ESR) was already higher at week 1 and thereafter at all time points through to week 24 in the certolizumab pegol arm vs placebo ($p<0.001$). The majority of adverse events were mild or moderate.

Long term efficacy of certolizumab

The long term efficacy and safety of certolizumab was evaluated in an eight-year study which included the participants of the FAST4WARD study. Four hundred and two patients taking 400 mg certolizumab every 4 weeks were included in this long-term study. The primary purpose was to obtain long-term efficacy and safety data of certolizumab treatment in patients with RA. The results showed a good sustainability of remission. Treatment with certolizumab pegol was associated with a rapid and consistent efficacy and with sustained improvements in disease activity and physical function up to 6 years (Fig. 4). Regarding safety, 24.9% of the participants were withdrawn due to adverse events (107).

Comparisons

Several studies have been performed to evaluate the efficacy of various biologic DMARDs *versus* placebo in the treatment of RA. Almost all of them have demonstrated that active treatment results in significant increases in the percentage of patients achieving ACR20, ACR50, ACR70 responses after six or twelve months of treatment.

On the other hand, there are no head-to-head comparisons between different anti-TNF-α therapies, while there are only two head-to-head comparisons between different anti-TNF-α therapies with other biologics (44, 45), and therefore their relative effectiveness and safety is hard to assess.

An alternative approach would be to perform indirect comparisons *versus* a common comparator (46). Some recently published papers employed multiple-treatment meta-analyses to compare the older marketed anti-TNFα agents (infliximab, etanercept, adalimumab) either to each other (47, 48) or to a different class biological agent (abatacept, anakinra, or rituximab) (49-51).

In the meta-analysis by Launois *et al*. (52), certolizumab was compared with 4 anti-TNF-α agents (infliximab, etanercept, adalimumab, golimumab) and 2 anti-interleukins (anakinra, tocilizumab). The aim of the above comparison was to establish or not the non-inferiority of the novel TNF-α blocker certolizumab. The meta-analysis was based on a selection of 19 placebo-controlled studies with similar protocols undertaken in patients receiving a concomitant conventional DMARD (essentially MTX). All active treatments demonstrated significant efficacy *versus* placebo in the ACR20 and ACR50 response criteria in all studies (except for golimumab, which showed no sig-

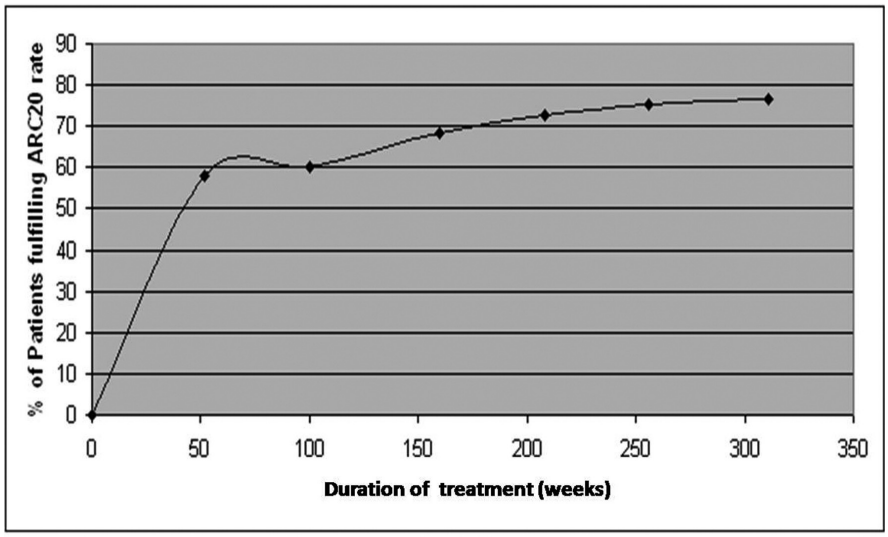

Fig. 4. Percentage of patients on long-term treatment with certolizumab achieving ACR20 response.

nificant efficacy regarding the ACR20 criteria in one study and infliximab which was not significantly efficacious regarding the ACR70 criteria in one study).The comparisons were carried out by a multiple-treatment Bayesian random-effects meta-analysis. It appears that certolizumab is non-inferior to the other TNF-α blockers. Another conclusion drawn from the meta-analysis by Launois is that anakinra has the lowest efficacy in terms of ACR response criteria. Besides, a couple of other meta-analyses have reached a similar conclusion concerning the superiority of anti-TNF-α agents in comparison with anakinra (49, 51).

Another meta-analysis was performed by Turkstra *et al*. (53) comparing the efficacy of nine biologic DMARDs via a mixed treatment comparison approach (54). The focus of this analysis was the short-term efficacy of nine biologic DMARDs (abatacept, adalimumab, anakinra, certolizumab, etanercept, golimumab, infliximab, rituximab and tocilizumab) in patients with established RA. Meta-analyses were performed on efficacy data (ACR20, ACR50, and ACR70) at approximately 6 months adjusting for differences between study characteristics and allowing indirect comparisons between treatments. The analyses were performed taking into account the recommended doses for each drug. The results showed that certolizumab is not inferior to the other biological treatments.

Safety

In general, safety analyses based on data from controlled and open-label clinical studies show that the safety profile of certolizumab appears comparable to that of other TNF-inhibitors when given in RA patients.

In 4 phase 3, placebo-controlled studies (34, 35, 43, 108), the majority of adverse events were mild to moderate, often self-limiting, and did not necessitate permanent withdrawal from treatment. The incidence of AEs did not differ between the 200 mg and 400 mg every 2 weeks dose regimens (67.8% and 67.1%, respectively), however patients who received certolizumab 400 mg every 4 weeks had the highest incidence of AEs (77.7%). A possible explanation is that the dose regimen of certolizumab 400 mg every 4 weeks was evaluated in 2 studies (43, 108) primarily conducted at sites in North America and Western Europe while the dose regimen of certolizumab 400 mg every 2 weeks was evaluated in the 2 RAPID studies (34, 35), which were primarily conducted at sites in Eastern Europe. Thus, differences in reporting adverse effects rather than the dosing regimen may have resulted for this observed difference.

The rate of infection was 0.91/patient-year in the certolizumab-treated patients and 0.72/patient-year in the placebo-treated patients. The infections consisted primarily of upper respiratory tract infections (including nasopharyngitis) and urinary tract infections AEs (34, 35). Infections were the most common serious adverse events reported in clinical trials with certolizumab. Cases of tuberculosis, pneumonia and erysipelas were recorded in patients receiving certolizumab plus MTX. In the 2 RAPID trials ten cases of tuberculosis were reported, which was commonly disseminated or extrapulmonary in nature. Of note, all occurred in countries with high incidence rates of the disease and insufficient stringency in screening for latent tuberculosis (34, 35). In the FAST4WARD trial, there were no reports of tuberculosis (43). These data suggest that certolizumab is associated with a significantly increased risk of opportunistic infections, particularly tuberculosis, which is expected for this class of drug. Thus, appropriate screening should be performed before the initiation of this anti-TNF treatment.

In a recent safety analysis (21) based on safety data from 6 placebo-controlled trials (32-35,43,108), which were summarised for a total of 1774 RA patients (n=640 for certolizumab 200 mg every 2 weeks plus MTX; n=635 for certolizumab 400 mg every 2 weeks plus MTX; n=278 for certolizumab 400 mg every 4 weeks; n=221 for other dosages of certolizumab), a greater percentage of patients in the pooled certolizumab dose group (5.0%) experienced adverse events leading to drug withdrawal compared to the placebo group (2.5%). Malignant neoplasms including solid tumours and lymphomas were reported among 12 patients in the 2 RAPID studies. They occurred at similar rates across the treatment groups. There were no reports of malignancy (including lymphoma) in FAST4WARD trial. In total, 9 deaths were recorded (seven deaths in RAPID 1 study and two deaths in RAPID 2) and they were considered either unlikely to be related or unrelated to certolizumab administration. The main events that lead to death were major cardiovascular events (such as myocardial infarction, cardiac arrest, atrial fibrillation, cerebral stroke and shock), hepatic neoplasm and femur fracture.

Additionally, an updated and long-term safety analysis of 4049 certolizumab-treated RA patients participating in 10 completed randomised controlled trials and several open-label extensions, that was recently published, did not raise any new or unexpected (for the class of TNF inhibitors) safety concerns (55). Of note, the incidence rate of the serious infectious events decreased with continued exposure to certolizumab, while the respective rate of opportunistic infections did not increase over time. The incidence rate of malignancy remained stable with prolonged exposure to certolizumab (55).

Conclusion

Certolizumab is a new anti-TNF-α biologic agent with an innovative molecular structure and unique pharmacodynamic and pharmacokinetic properties that has recently been approved for the treatment of RA patients for whom treatment with traditional DMARDs has failed. So far, efficacy and safety data are mainly derived from controlled clinical trials, which suggest that certolizumab offers significant clinical and radiographic benefits to RA patients. At the same time it exhibits an acceptable safety profile, comparable to that of other TNF-α blockers. Its overall positive benefit-to-risk ratio, as well as its swift onset of action suggests that this novel TNF-α blocker presents an attractive alternative when considering the next treatment option for patients with moderate to severe RA despite treatment with DMARDs.

References

1. ALAMANOS Y, VOULGARI PV, DROSOS AA: Incidence and prevalence of rheumatoid arthritis, based on the 1987 American College of Rheumatology criteria: a systematic review. *Semin Arthritis Rheum* 2006; 36: 182-8.
2. ALAMANOS Y, DROSOS AA: Epidemiology of adult rheumatoid arthritis. *Autoimmun Rev* 2005; 4: 130-6.
3. SYMMONS D, TURNER G, WEBB R *et al*.: The prevalence of rheumatoid arthritis in the United Kingdom: new estimates for a new century. *Rheumatology* 2002; 41: 793-800.
4. SOKKA T, ABELSON B, PINCUS T: Mortality in rheumatoid arthritis: 2008 update. *Clin Exp Rheumatol* 2008; 26 (Suppl. 51): S35-61.
5. STRAND V, KHANNA D: The impact of rheumatoid arthritis and treatment on patients' lives. *Clin Exp Rheumatol* 2010; 28 (Suppl. 59): S32-40.
6. CASTREJON I, PINCUS T: Patient self-report outcomes to guide a treat-to-target strategy in clinical trials and usual clinical care of rheumatoid arthritis. *Clin Exp Rheumatol* 2012; 30 (Suppl. 73): S50-5.
7. TURCHETTI G, SMOLEN JS, KAVANAUGH A *et al*.: Treat-to-target in rheumatoid arthritis: clinical and pharmacoeconomic considerations. Introduction. *Clin Exp Rheumatol* 2012; 30 (Suppl. 73): S1.
8. KEFFER J, PROBERT L, CAZLARIS H *et al*.: Transgenic mice expressing human tumour necrosis factor: a predictive genetic model of arthritis. *EMBO J* 1991; 10: 4025-31.
9. SMOLEN JS, REDLICH K, ZWERINA J *et al*.: Pro-inflammatory cytokines in rheumatoid arthritis: pathogenetic and therapeutic aspects. *Clin Rev Allergy Immunol* 2005; 28: 239-48.
10. AGGARWAL BB: Signalling pathways of the TNF superfamily: a double-edged sword. *Nat Rev Immunol* 2003; 3: 745-56.
11. VANDENABEELE P, DECLERCQ W, BEYAERT R *et al*.: Two tumour necrosis factor receptors: structure and function. *Trends Cell Biol* 1995; 5: 392-9.
12. SHIBATA J, GOTO H, ARISAWA T *et al*.: Regulation of tumour necrosis factor (TNF) induced apoptosis by soluble TNF receptors in Helicobacter pylori infection. *Gut* 1999; 45: 24-31.
13. NESBITT AM, STEPHENS S, CHARTASH EK: Certolizumab pegol: a PEGylated anti-tumour necrosis factor alpha biological agent. *In* VERONESE FM (Ed.) PEGylated Protein Drugs: *Basic Science and Clinical Applications*. Birkhäuser Verlag/Switzerland 2009, pp 229-231.
14. HSU H, SHU HB, PAN MG *et al*.: TRADD–TRAF2 and TRADD–FADD interactions define two distinct TNF receptor 1 signal transduction pathways. *Cell* 1996; 84: 299-308.
15. TARTAGLIA LA, WEBER RF, FIGARI IS *et al*.: The two different receptors for tumor necrosis factor mediate distinct cellular responses. *Proc Natl Acad Sci USA* 1991; 88: 9292-6.
16. TADA Y, HO A, KOARADA S *et al*.: Collagen-induced arthritis in TNF receptor-1-deficient mice: TNF receptor-2 can modulate arthritis in the absence of TNF receptor-1. *Clin Immunol* 2001; 99: 325-33.
17. ARMAKA M, APOSTOLAKI M, JACQUES P *et al*.: Mesenchymal cell targeting by TNF as a common pathogenic principle in chronic inflammatory joint and intestinal diseases. *J Exp Med* 2008; 205: 331.
18. ZHANG YH, HEULSMANN A, TONDRAVI MM *et al*.: Tumor necrosis factor-alpha (TNF) stimulates RANKL-induced osteoclastogenesis via coupling of TNF type 1 receptor and RANK signaling pathways. *J Biol Chem* 2001; 276: 563-8.
19. KOBAYASHI K, TAKAHASHI N, JIMI E *et al*.: Tumor necrosis factor alpha stimulates osteoclast differentiation by a mechanism independent of the ODF/RANKL-RANK interaction. *J Exp Med* 2000; 191: 275-86.
20. WEIR N, ATHWAL D, BROWN D *et al*.: A new generation of high-affinity humanized PEGylated Fab' fragment anti-tumor necrosis factor-α monoclonal antibodies. *Therapy* 2006; 3: 535-45.
21. Australian Public Assessment Report for Certolizumab pegol TGA Health Safety Regulation February 2010.
22. NESBITT A, FOSSATI G, BERGIN M *et al*.: Mechanism of action of certolizumab pegol (CDP870): *in vitro* comparison with other anti-tumor necrosis factor alpha agents. *Inflamm Bowel Dis* 2007; 13: 1323-32.
23. PALFRAMAN R, AIREY M, MOORE A *et al*.: 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* 2009; 348: 36-41.
24. HENRY AJ, KENNEDY J, FOSSATI G *et al*.: Stoichiometry of binding to and complex formation with TNF by certolizumab pegol, adalimumab, and infliximab, and the biologic effects of these complexes. *Gastroenterology* 2007; 132 (4 Suppl. 2): A231.
25. FOSSATI G, NESBITT AM: Reverse signalling of membrane TNF in human natural killer cells: a comparison of the effect of certolizumab pegol and other anti-TNF agents. *J Translational Med* 2011; 9 (Suppl. 2): O3.
26. HENRY AI, GONG H, NESBITT AM: Mapping the certolizumab pegol epitope on TNF and comparison with infliximab, adalimumab and etanercept. *J Translational Med* 2011; 9 (Suppl. 2): P43.
27. BURNHAM NL: Polymers for delivering peptides and proteins. *Am J Hosp Pharm* 1994; 51: 210-8.
28. HARRIS JM, CHESS RB: Effect of pegylation on pharmaceuticals. *Nat Rev Drug Discov* 2003; 2: 214-21.
29. CHAPMAN AP: PEGylated antibodies and antibody fragments for improved therapy: a review. *Adv Drug Deliv Rev* 2002; 54: 531-54.
30. HEATHFIELD SK, PARKER B, ZEEF LA *et al*.: Certolizumab pegol attenuates the pro-inflammatory state in endothelial cells in a manner that is atheroprotective. *Clin Exp Rheumatol* 2013; 31: 225-33.
31. PARTON T, KING L, PARKER G *et al*.: The PEG moiety of certolizumab pegol is rapidly cleared from the blood of humans by the kidneys once it is cleaved from the Fab'. *Ann Rheum Dis* 2009; 68: 189.
32. CHOY EH, HAZLEMAN B, SMITH M *et al*.: Efficacy of a novel PEGylated humanized anti-TNF fragment (CDP870) in patients with rheumatoid arthritis: a phase II double-blinded, randomized, dose-escalating trial. *Rheumatology* 2002; 41: 1133-7.
33. KEYSTONE E, CHOY E, KALDEN *et al*.: CDP870, a novel, PEGylated humanised TNF-inhibitor is effective in treating the signs and symptoms of rheumatoid arthritis. *Arthritis Rheum* 2001; 44: 2946.
34. KEYSTONE E, HEIJDE DV, 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.
35. 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.
36. CURTIS JR, LUIJTENS K, KAVANAUGH A: Predicting future response to certolizumab pegol in rheumatoid arthritis patients: Features at 12 weeks associated with low disease activity at 1 year. *Arthritis Care Res* (Hoboken) 2012; 64: 658-67.
37. PINCUS T, FURER V, KEYSTONE E *et al*.: RAPID3 (Routine Assessment of Patient Index Data 3) severity categories and response criteria: Similar results to DAS28 (Disease Activity Score) and CDAI (Clinical Disease Activity Index) in the RAPID 1 (Rheumatoid Arthritis Prevention of Structural Damage) clinical trial of certolizumab pegol. *Arthritis Care Res* (Hoboken) 2011; 63: 1142-9.
38. CURTIS JR, CHEN L, LUIJTENS K *et al*.: Dose escalation of certolizumab pegol from 200 mg to 400 mg every other week provides no additional efficacy in rheumatoid arthritis: an analysis of individual patient-level data. *Arthritis Rheum* 2011; 63: 2203-8.
39. KEYSTONE EC, CURTIS JR, FLEISCHMANN RM *et al*.: Rapid improvement in the signs and symptoms of rheumatoid arthritis following certolizumab pegol treatment predicts better long term outcomes: post-hoc analysis of a randomized controlled trial. *J Rheumatol* 2011; 38: 990-6.
40. 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 Rheum* 2009; 61: 1592-600.
41. STRAND V, SMOLEN JS, VAN VOLLENHOVEN RF *et al*.: Certolizumab pegol plus methotrexate provides broad relief from the burden of rheumatoid arthritis: analysis of patient-reported outcomes from the RAPID 2 trial. *Ann Rheum Dis* 2011; 70: 996-1002.
42. WEINBLATT ME, FLEISCHMANN R, HUIZINGA TW *et al*.: Efficacy and safety of certolizumab pegol in a broad population of patients with active rheumatoid arthritis: results from the REALISTIC phase IIIb study. *Rheumatology* (Oxford) 2012;51:2204-14.
43. 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.
44. GABAY C, EMERY P, VAN VOLLENHOVEN R *et al*.: Tocilizumab monotherapy versus adalimumab monotherapy for treatment of rheumatoid arthritis (ADACTA): a randomised, double-blind, controlled phase 4 trial. *Lancet* 2013; 381: 1541-50.
45. WEINBLATT ME, SCHIFF M, VALENTE R *et al*.: Head-to-head comparison of subcutaneous abatacept versus adalimumab for rheumatoid arthritis: findings of a phase IIIb, multinational, prospective, randomized study. *Arthritis Rheum* 2013; 65: 28-38.
46. SUTTON A, ADES AE, COOPER N *et al*.: Use of indirect and mixed treatment comparisons for technology assessment. *Pharmacoeconomics* 2008; 26: 753-67.
47. KRISTENSEN LE, CHRISTENSEN R, BLIDDAL H *et al*.: The number needed to treat for adalimumab, etanercept, and infliximab based on ACR50 response in three randomized controlled trials on established rheumatoid arthritis: a systematic literature review. *Scand J Rheumatol* 2007; 36: 411-7.
48. ALONSO-RUIZ A, PIJOAN JI, ANSUATEGUI E *et al*.: Tumor necrosis factor alpha drugs in rheumatoid arthritis: systematic review and metaanalysis of efficacy and safety. *BMC Musculoskelet Disord* 2008; 9: 52.
49. NIXON R, BANSBACK N, BRENNAN A: The efficacy of inhibiting tumour necrosis factor alpha and interleukin 1 in patients with rheumatoid arthritis: a meta-analysis and adjusted indirect comparisons. *Rheumatology* 2007; 46: 1140-7.
50. VENKATESHAN SP, SIDHU S, MALHOTRA S *et al*.: Efficacy of biologicals in the treatment of rheumatoid arthritis: a meta-analysis. *Pharmacology* 2009; 83: 1-9.
51. SINGH JA, WELLS GA, CHRISTENSEN R *et al*.: Biologics for rheumatoid arthritis: an overview of Cochrane reviews. *Cochrane Database Syst Rev* 2009; 4: CD007848.
52. LAUNOIS R, AVOUAC B, BERENBAUM F *et al*.: Comparison of Certolizumab pegol with other anticytokine agents for treatment of rheumatoid arthritis: a multiple-treatment bayesian metaanalysis. *J Rheumatol* 2011; 38: 835-45.
53. TURKSTRA E, NG SK, SCUFFHAM PA: A mixed treatment comparison of the short-term efficacy of biologic disease modifying anti-rheumatic drugs in established rheumatoid arthritis. *Curr Med Res Opin* 2011; 27: 1885-97.
54. LU G, ADES AE: Combination of direct and indirect evidence in mixed treatment comparisons. *Stat Med* 2004; 23: 3105-24.
55. BYKERK VP, CUSH J, WINTHROP K *et al*.: Update on the safety profile of certolizumab pegol in rheumatoid arthritis: an integrated analysis from clinical trials. *Ann Rheum Dis* 2013 Oct 3 [Epub ahead of print].

Websites

101. REMICADE SUMMARY OF PRODUCT CHARACTERISTICS http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Summary_for_the_public/human/000240/WC500050883.pdf
102. ENBREL SUMMARY OF PRODUCT CHARACTERISTICS http://www.ema.europa.eudocs/en_GB/document_library/EPAR__Product_Information/human/000262/WC500027361.pdf
103. HUMIRA SUMMARY OF PRODUCT CHARACTERISTICS http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_Product_Information/human/000481/WC500050870.pdf
104. SIMPONI SUMMARY OF PRODUCT CHARACTERISTICS http://www.ema.europa.eu/docs/en_GB/document_library/EPAR__Summary_for_the_public/human/000992/WC500052370.pdf
105. CIMZIA SUMMARY OF PRODUCT CHARACTERISTICS http://www.ema.europa.eu/ docs/en_GB/document_library/EPAR__Product_Information/human/001037/WC500069763.pdf
106. http://clinicaltrials.gov/ct2/show/results/NCT00160693?sect=X0125#all
107. http://clinicaltrials.gov/ct2/show/NCT00717236
108. http://www.ucb.com/_up/ucb_com_patients/documents/C87014_CSS_20080604.pdf