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ADIS DRUG EVALUATION

Certolizumab Pegol

A Review of Its Use in the Management of Rheumatoid Arthritis

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Abstract Certolizumab pegol (Cimzia®) is a recombinant, polyethylene glycolylated, antigen-binding fragment of a humanized monoclonal antibody that selectively targets and neutralizes tumour necrosis factor (TNF)-α. The drug is indicated for subcutaneous use every 2 or 4 weeks (q2w or q4w) for the treatment of adults with moderate to severe active rheumatoid arthritis (RA). The efficacy of subcutaneous certolizumab pegol in adults with active RA has been investigated in several well designed, placebo-controlled trials. In four pivotal studies of ≤52 weeks duration, patients with moderate to severe disease receiving recommended dosages of certolizumab pegol (200 mg q2w or 400 mg q4w), either as monotherapy (after failing prior disease-modifying anti-rheumatic drug [DMARD] therapy) or in combination with methotrexate (after responding inadequately to methotrexate alone), experienced rapid clinical improvement, with some combination trials also demonstrating inhibition of radiographic progression. The beneficial effects of certolizumab pegol therapy were generally maintained for up to ≈5 years in clinical trial extensions in which the drug was administered at dosages of 400 mg q4w or q2w. Additional studies suggest certolizumab pegol is also effective in patients who are Asian or have low to moderate disease activity, as well as more clinically representative patient populations. The tolerability profile of certolizumab pegol was acceptable, with infections/infestations the most common adverse events. Thus, certolizumab pegol is an effective option for the management of active RA in adults, although additional long-term and comparative efficacy and tolerability data are needed to help definitively position certolizumab pegol relative to other biological DMARDs, particularly other anti-TNF agents.

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1 Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune disease that predominantly affects the synovial membrane of the joints, causing cartilage and bone erosion, although tendons, muscle and connective and fibrous tissues may also be affected [1, 2]. Onset is often between the ages of 30 and 55 years [3], with the first year of disease usually being associated with the fastest rate of joint erosion [1]. It is a disabling condition typically associated with pain, swelling and redness of the joints, early morning stiffness and fatigue, with at least half of affected individuals in developed countries no longer being able to work full time within 10 years of RA onset [1, 2, 4]. RA also carries an increased mortality risk, with ≈40 % of the deaths being the result of cardiovascular causes [1].

Corticosteroids, NSAIDs and other analgesics may be used to provide relief from RA symptoms [4, 5], although the mainstay pharmacological option for RA management is disease-modifying anti-rheumatic drugs (DMARDs) [6], which can potentially alter the course of disease by halting, or at least slowing, its progression [4, 7]. The more traditional DMARDs (e.g. methotrexate, leflunomide, sulfasalazine and hydroxychloroquine) are nonbiological agents thought to act via nonspecific immunosuppressive,

anti-inflammatory and cytotoxic mechanisms [7, 8]. More recently, advances in the understanding of RA pathogenesis have facilitated the development of a range of biological DMARDs that act by targeting specific mediators of the disease, such as the pro-inflammatory cytokine tumour necrosis factor (TNF)-α [7]. TNFα is present at high levels in rheumatoid joints [9] and plays a key role in RA pathogenesis through effects such as induction of cytokine and chemokine expression, angiogenesis promotion, synovial fibroblast protection and pain induction [10].

One of the more recent biological DMARDs is certolizumab pegol (Cimzia®), a recombinant antigen-binding fragment (Fab′) of a humanized antibody against TNFα, conjugated to a polyethylene glycol (PEG) moiety of ≈40 kDa [11, 12]. The drug is administered subcutaneously and is indicated for the treatment of RA in a number of countries, including the US [11] and those of the EU [12]. It is also approved for the treatment of Crohn's disease in some countries, including the US [11]. This article reviews the pharmacological, clinical efficacy and tolerability data relevant to the use certolizumab pegol in patients with RA.

Data sources: Medical literature (including published and unpublished data) on 'certolizumab pegol' was identified by searching databases (including MEDLINE and EMBASE) for articles published since 1996 to 17 December 2012, bibliographies from published literature, clinical trial registries/databases and websites (including those of regional regulatory agencies and the manufacturer). No language restrictions were applied. Additional information (including contributory unpublished data) was also requested from the company developing the drug.

Search terms: ('certolizumab pegol' or 'certolizumab') and 'rheumatoid arthritis'.

Study selection: Studies in patients with rheumatoid arthritis who received certolizumab pegol. Inclusion of studies was based mainly on the methods section of the trials. When available, large, well designed, comparative trials with appropriate statistical methodology were preferred. Relevant pharmacodynamic and pharmacokinetic data are also included.

Keywords: Certolizumab pegol, rheumatoid arthritis, pharmacodynamics, pharmacokinetics, therapeutic use, tolerability.

2 Pharmacodynamic Properties

This section provides an overview of the key pharmacodynamic properties of certolizumab pegol, which have been reviewed in detail previously [13]. Some data are available as abstracts [14–16] or from the US [11] or EU [12] prescribing information or the US FDA pharmacology review [17].

Certolizumab pegol is a PEGylated, recombinant Fab′ fragment of a humanized anti-TNFα monoclonal antibody that acts by selectively binding to TNFα, thus preventing it from interacting with its cell surface receptors (p55 and p75) [11, 17, 18]. The affinity of the drug for human TNFα in vitro is high (mean dissociation constant [KD] ≈90 pmol/L) and greater than that of some other anti-TNFα agents, namely adalimumab and infliximab, but not etanercept (respective mean KD values of 158, 229 and 33 pmol/L) [17]. Certolizumab pegol neutralizes TNFα (concentration required to inhibit human TNFα by 90 % in vitro was 4 ng/mL) but not TNFβ [11, 12], and displays concentration-dependent neutralization of both soluble and membrane-bound human TNFα in vitro [19].

Lipopolysaccharide-induced production of TNFα [17] and another proinflammatory cytokine, interleukin (IL)-1β [17, 19], by human monocytes was inhibited by certolizumab pegol in vitro (mean concentrations required to achieve 50 % inhibition of 0.09 and 0.19 ng/mL, where specified [17]), with the drug demonstrating greater potency in this regard than infliximab, adalimumab and etanercept.

In contrast to these and other anti-TNF agents, certolizumab pegol does not contain an IgG fragment crystallizable (Fc) [i.e. constant] region and, as a result, does not mediate complement-dependent cytotoxicity (CDC) or antibody-dependent cell-mediated cytotoxicity (ADCC) in vitro [19]. Further in vitro data indicate that, unlike infliximab, adalimumab and etanercept, certolizumab pegol does not induce apoptosis of activated human monocytes or peripheral blood lymphocytes (PBLs) or result in degranulation or loss of cell membrane integrity in polymorphonuclear cells [19]. Moreover, the PEG moiety of certolizumab pegol appears to inhibit non-immune-stimulated degranulation of mast cells, at least in vitro [14], which may explain the low incidence of injection-site pain associated with the drug in patients with RA (Sect. 5.1), given that such pain may be related to the inflammatory mediators released when mast cells degranulate.

Rapid reductions in C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), which are both acute-phase reactants of inflammation, were observed in patients with moderate to severe active RA who received treatment with subcutaneous certolizumab pegol at a maintenance dosage of 200 or 400 mg every 2 weeks (q2w) or 400 mg every 4 weeks (q4w), either as monotherapy or in combination with methotrexate, in four large placebo-controlled trials (further data from these studies are discussed in Sect. 4) [20–23].

TNF-mediated chronic inflammation may contribute to the accelerated atherosclerosis and premature cardiovascular mortality associated with RA, by promoting the activation and dysfunction of endothelial cells and their recruitment of leukocytes. In vitro data suggest that certolizumab pegol may attenuate TNF-mediated upregulation of certain endothelial cell adhesion molecules (intercellular adhesion molecule-1, vascular cell adhesion molecule-1 and E-selectin) [15]. However, whether this property translates to improved endothelial function in the clinical setting requires investigation.

Antibodies against certolizumab pegol may develop during treatment with the drug. In placebo-controlled studies, overall, ≈7 % of patients with RA had detectable anti-certolizumab pegol antibodies on at least one occasion, and of these patients, approximately one third had antibodies that were neutralizing in vitro [11, 12]. However, the rate of neutralizing antibody formation across trials was fourfold lower among patients who received certolizumab pegol in combination with methotrexate than among those who received certolizumab pegol as monotherapy (2 vs. 8 %) [11]. The presence of anti-certolizumab pegol antibodies was associated with a lower concentration of certolizumab pegol in plasma (due to elevated clearance; Sect. 3.1) and reduced clinical benefit (Sect. 4.1.1 and 4.2.1), although was not associated with adverse events [11].

When certolizumab pegol was assessed for cross-reactivity across a panel of 37 normal human tissues, none was detected [17]. Moreover, a single 400 mg subcutaneous dose of the drug had no effect on semen quality over a follow-up period of 14 weeks when compared with placebo in a double-blind trial conducted in 20 healthy male subjects [16].

3 Pharmacokinetic Properties

This section provides a brief overview of the pharmacokinetics of certolizumab pegol, which have been reviewed previously [13]. Patient populations and dosage details are reported where available. Some data are sourced from abstracts [24–26] or the US [11] or EU [12] prescribing information.

Certolizumab pegol displayed predictable, linear, dose-related pharmacokinetics following administration of single subcutaneous doses of up to 800 mg in healthy volunteers [11]. The mean maximum plasma concentration (C_{max}) of the drug at week 5 of the recommended subcutaneous dosage regimen (400 mg loading dose at weeks 0, 2 and 4, then 200 mg q2w) was ≈43–49 μg/mL [11]. Certolizumab pegol reached C_{max} between 54 and 171 h after subcutaneous injection and had a bioavailability of ≈80 % (range of 76–88 %) [11, 12]. Certolizumab pegol was estimated to have an apparent volume of distribution of 8 L in patients with RA in a population pharmacokinetic analysis [12].

Limited data from studies in which a single subcutaneous dose of certolizumab pegol 400 mg was administered to healthy volunteers (total $n = 16$) indicated that the PEG moiety, once cleaved from the Fab′ fragment, does not undergo further metabolism and is eliminated rapidly via the kidneys [24].

Certolizumab pegol has a terminal elimination half-life of ≈14 days and, according to data from a population pharmacokinetic analysis in patients with RA, has an estimated clearance of 21 mL/h after subcutaneous administration (inter-subject and inter-occasion variability of 30.8 % and 22.0 %) [11, 12].

3.1 Special Patient Groups and Drug Interactions

Among various patient characteristics assessed to determine their potential effect on the pharmacokinetics of certolizumab pegol in a population pharmacokinetic analysis in patients with RA or Crohn's disease, only bodyweight and antibodies against certolizumab pegol appeared to have a significant effect [11]. Bodyweight and certolizumab pegol exposure are inversely related [11], with the clearance of the drug being 29 % lower in patients weighing 40 kg and 38 % higher in patients weighing 120 kg compared with a patient of 70 kg [12]; however, weight-adjusted dosage regimens are not expected to provide any additional benefit based on data from a pharmacodynamic exposure-response analysis [11]. In the presence of anti-certolizumab pegol antibodies, clearance of the drug was increased up to 3.6-fold [11, 12].

Population pharmacokinetic data suggest that the pharmacokinetics of certolizumab pegol are not affected by age, gender, race or mild renal impairment, although data in patients with moderate and severe renal impairment are currently insufficient for dosage recommendations to be provided; studies specifically evaluating the pharmacokinetics of certolizumab pegol in individuals with renal or hepatic impairment have not yet been conducted [11, 12].

Placental transfer of certolizumab pegol was low among ten women with inflammatory bowel disease who were treated with the drug during pregnancy [25]. Although the clinical significance of these findings is currently unclear, limited data from an analysis of the global certolizumab pegol safety database suggested that outcomes of pregnancies that involved direct exposure to the drug ($n = 139$) were consistent with those in the general population [26]. However, certolizumab pegol is not recommended for use during pregnancy in the EU as the immune responses of the newborn may be affected [12]; similarly, in the US,

certolizumab pegol should be used during pregnancy only if clearly necessary [11].

The pharmacokinetics of certolizumab pegol were not affected by concomitant use of methotrexate, corticosteroids, NSAIDs or other analgesics in a population pharmacokinetic analysis [12], and coadministration of certolizumab pegol with methotrexate in patients with RA in a drug interaction study had no effect on the pharmacokinetics of methotrexate (whether certolizumab pegol pharmacokinetics were affected was not evaluated) [11]. However, therapeutic plasma levels of certolizumab pegol are more likely to be sustained in patients receiving the drug in combination with methotrexate, as the incidence of anti-certolizumab pegol antibodies (which can impact on the efficacy of the drug; see Sect. 4) is lower [11]. Certolizumab pegol has yet to be coadministered with corticosteroids, immunosuppressants, NSAIDs and other analgesics in formal drug interaction studies [11].

4 Therapeutic Efficacy

This section focuses on the efficacy of subcutaneous certolizumab pegol as monotherapy (Sect. 4.1) or in combination with methotrexate (Sect. 4.2) in adults with moderate to severe active RA, as evaluated in four double-blind clinical trials (see Table 1 for inclusion/exclusion criteria). Data from additional analyses and open-label extensions of these pivotal studies are also available (Sect. 4.1 and 4.2). Each of these trials permitted concurrent use of oral corticosteroids (equivalent to prednisone ≤10 mg/day, provided the dosage had been stable for ≥4 weeks) [20–23] as well as NSAIDs [20–22] (provided dosage had been stable for 2 weeks) [23], and some also allowed use of other analgesics [20, 22]. All DMARDs (other than methotrexate in combination-therapy trials [21–23]) were discontinued ≥28 days (or five drug half-lives) before baseline [22, 23] or initiating study drug [20, 21], although leflunomide had to have been discontinued 6 months previously unless washed out with cholestyramine, where specified [20, 22, 23]. Results of several other double-blind trials, including studies in Asian patients (Sect. 4.3), patients with low to moderate disease activity (Sect. 4.4.1) and patients representative of clinical practice (Sect. 4.4.2) are also discussed, along with data from observational studies (Sect. 4.4.3).

The primary efficacy measure in double-blind trials was the proportion of patients achieving >20 % improvement in arthritis symptoms (according to American College of Rheumatology [ACR] criteria [i.e. ACR20 response]) [20–23, 27–31] or achieving remission (according to clinical disease activity index [CDAI] criteria) [32]; one trial included radiographic progression, evaluated by modified total Sharp score (mTSS), as a coprimary efficacy measure [22]. Data for all evaluated maintenance dosages of certolizumab pegol, including those recommended for use (i.e. 200 mg q2w and 400 mg q4w; Sect. 6) are discussed in this section for completeness. Some data are available as abstracts [27–30, 32–47] or from the US prescribing information [11].

4.1 Monotherapy

The efficacy of certolizumab pegol 400 mg q4w as monotherapy (without a recommended prior loading dose; Sect. 6) in adults with moderate to severe active RA for whom at least one prior DMARD has failed (due to intolerance or lack of efficacy) has been compared with that of placebo in a 24-week, randomized, double-blind, multicentre trial known as FAST4WARD (eFficAcy and Safety of cerTolizumab pegol 4 Weekly dosAge in RheumatoiD arthritis) [20] [see Fig. 1 for details]. Overall, patients had a mean disease duration of ≈9.6 years, a mean Disease Activity Index Score 28 (DAS28)-ESR of 6.3 and had received a mean of two DMARDs previously, with most (≈82 % of patients) having received prior methotrexate therapy. Patients who completed this trial or discontinued at, or after, 12 weeks (for reasons other than noncompliance or treatment-related adverse events) could enter an open-label extension of certolizumab pegol at the same dosage (other DMARDs were also permitted [46]); also eligible to participate in this extension were patients who completed or withdrew from a 24-week combination-therapy study comparing certolizumab pegol 400 mg q4w plus methotrexate with placebo plus methotrexate (Sect. 4.2) [21].

4.1.1 Clinical Outcomes

Monotherapy with certolizumab pegol 400 mg q4w was effective in improving the clinical signs and symptoms of moderate to severe active RA in adults who had failed at least one prior DMARD. Compared with placebo, certolizumab pegol was associated with significantly higher ACR20 (primary endpoint), ACR50 and ACR70 response rates (Fig. 1) and also significantly ($p \leq 0.05$) improved each of the individual core components of the ACR response after 24 weeks of treatment [20]. Of note, ACR20 response rates were 1.7-fold lower in certolizumab pegol recipients who tested positive for antibodies against the drug than in those who tested negative (33 vs. 56 %) [11].

The onset of therapeutic action of certolizumab pegol was rapid, with the drug demonstrating significant ($p \leq 0.05$) benefit over placebo after only 1 week of treatment for the above parameters, with the exception of ACR70, which did not significantly favour the

Table 1 Key inclusion/exclusion criteria of pivotal clinical trials of certolizumab pegol [20–23]

Eligibility	Criteria
Inclusion	Aged ≥18 years [20–23] (with an upper limit of 75 years [20, 21])
	RA (as defined by American College of Rheumatology criteria) for ≥6 months [20–23] but ≤15 years [22, 23]
	Active disease (defined as ≥9 tender joints and ≥9 swollen joints, together with one or more of the following: ≥45 min morning stiffness [20, 21], a C-reactive protein level >10 [20, 21] or >15 [22, 23] mg/L, an erythrocyte sedimentation rate ≥28 [20, 21] or ≥30 [22, 23] mm/h
Exclusion	Inflammatory arthritis other than RA [20–23] or a secondary noninflammatory arthritis [22, 23]
	Prior TB [20–23], current radiographic evidence of TB [20, 21, 23] (active or latent) [22] or a positive PPD skin test [20–23][a]
	History of chronic, serious or life-threatening infection [20, 21, 23], current infection [20, 21, 23] or high risk of infection [22, 23]
	Treatment with biological therapy for RA in last 6 months [20–23], or etanercept and/or anakinra in last 3 months [22, 23], or severe hypersensitivity/anaphylactic reaction to prior biological therapy [22, 23]
	Prior treatment with [20, 21], or no response to [22, 23], anti-TNFα agents

PPD purified protein derivatives, *RA* rheumatoid arthritis, *TB* tuberculosis, *TNF*α tumour necrosis factor-α

[a] Patients with a positive PPD associated with previous Bacille Calmette–Guérin vaccination and without clinical/radiographic evidence of TB were eligible [20, 22, 23]

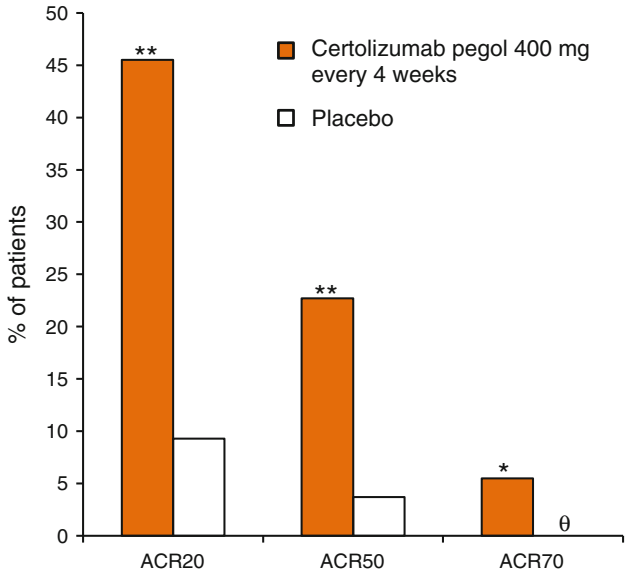

Fig. 1 Clinical efficacy of subcutaneous certolizumab pegol monotherapy in adults with moderate to severe active rheumatoid arthritis for whom previous disease-modifying anti-rheumatic drug(s) were unsuccessful. Proportion of patients who, after 24 weeks' treatment, achieved a 20 % (primary endpoint), 50 % or 70 % improvement from baseline in rheumatoid arthritis signs and symptoms (according to American College of Rheumatology criteria) in a randomized, double-blind trial (FAST4WARD) [20] in which patients received certolizumab pegol 400 mg ($n = 111$) or placebo ($n = 109$) every 4 weeks. Data are for the modified intent-to-treat population. *ACR20, 50 and 70* 20 %, 50 % and 70 % improvement in American College of Rheumatology criteria; *$p \leq 0.05$, **$p < 0.001$ versus placebo; θ 0 % response rate

certolizumab pegol group until week 8 [20]. Disease activity, as measured by DAS28-ESR, was also rapidly reduced with certolizumab pegol, with mean changes from baseline significantly ($p < 0.001$) favouring certolizumab pegol over placebo from week 1 of treatment onwards, including at week 24 (−1.5 vs. −0.6; mean baseline values were 6.3 in each group).

The clinical improvements seen after 24 weeks of treatment with certolizumab pegol monotherapy were generally sustained for up to ≈2 years of therapy in an extension [33] of this trial [20], with ACR20 and ACR50 response rates of 70.3 % and 34.4 % reported at 112 weeks among the 69 certolizumab pegol recipients who completed the initial trial and continued to receive the drug during the extension.

Longer-term data from this extension [46] also showed continued benefit of certolizumab pegol therapy on disease activity. DAS28-CRP was reduced (i.e. improved) from 4.38 at the start of the extension to 2.98 at 280 weeks (≈5.4 years) among patients who were originally randomized to receive the drug as monotherapy (in FAST4-WARD [20]) or in combination with methotrexate (in the 24-week RA-III study [21]) and continued to receive these regimens in the extension ($n = 210$ entered). Improvements in disease activity were also seen among patients ($n = 192$) who had received a corresponding placebo regimen in one of the initial studies and were switched to certolizumab pegol therapy for the extension (DAS28-CRP of 5.13 at extension baseline vs. 3.12 at 280 weeks).

4.1.2 Health-Related Quality of Life and Other Outcomes

Certolizumab pegol monotherapy improved health-related quality of life (HR-QOL), as measured by the Short Form-36 health survey (SF-36). Compared with placebo, the drug was associated with significant ($p < 0.001$) improvements in all eight SF-36 domain scores, as well as the mental and physical component summary (MCS and PCS) scores, after 24 weeks of therapy, with post hoc analyses suggesting that significantly ($p \leq 0.01$) more certolizumab pegol than

placebo recipients had achieved minimal clinically important differences in these parameters (some quantitative data were not reported) [20].

Recipients of certolizumab pegol also reported significant ($p < 0.001$) improvements in physical function, arthritis pain and fatigue relative to placebo recipients after 24 weeks of treatment, as indicated by mean changes from baseline in Health Assessment Questionnaire-Disability Index (HAQ-DI), visual analogue scale (VAS) and Fatigue Assessment Scale (FAS) scores, respectively [20]. Clinically meaningful improvements in these measures were seen in significantly ($p < 0.001$) more certolizumab pegol than placebo recipients when analysed post hoc (46–49 vs. 12–17 %) [20].

Treatment with certolizumab pegol may also have beneficial effects on productivity in the home and participation in activities, as measured by the RA-specific Work Productivity Survey (WPS-RA), according to analyses conducted in patients participating in the extension [34] of this trial. For example, among certolizumab pegol monotherapy recipients who completed FAST4WARD and continued to receive the drug as monotherapy throughout the extension ($n = 26$–46), the mean monthly number of household work days missed, days with reduced household productivity, and days of family/social/leisure activities missed was 2.7- to 5.6-fold lower at the start of the extension (i.e. after 24 weeks' treatment) and 7.9- to 31-fold lower after 268 weeks of therapy, than at baseline. Similar benefits were seen in an analysis that included all patients who completed 24 weeks' treatment with certolizumab pegol, either as monotherapy (in FAST4WARD [20]) or in combination with methotrexate (in the 24-week RA-III trial [21]), and entered the extension ($n = 95$–171) [34].

4.2 In Combination with Methotrexate

In adults with moderate to severe active RA despite ≥6 months' treatment with methotrexate, the efficacy of adding certolizumab pegol to the regimen has been compared with that of adding placebo in three randomized, double-blind, multicentre trials of 24 [21, 23] or 52 [22] weeks' duration (see Fig. 2 for details). Two of these studies (known as RAPID [Rheumatoid Arthritis PreventIon of structural Damage]-1 [22] and -2 [23]) used certolizumab pegol dosage regimens that incorporated loading doses, whereas the third trial [21] (referred to as RA-III in the US prescribing information [11]) did not (see Fig. 2). In RAPID-1 and -2, patients who did not achieve an ACR20 response after 12 and 14 weeks of treatment were withdrawn at week 16 (i.e. mandatory escape, as per protocol); these patients, as well as patients who completed the trials, were eligible to enter an extension to receive open-label treatment with certolizumab pegol plus methotrexate [22, 23]. Similarly, patients who completed RA-III or withdrew after 12 weeks (for reasons other than tolerability or non-compliance) could enter an open-label extension [21]; also eligible for this extension were patients who had completed or withdrawn from a 24-week monotherapy trial [20] (see Sect. 4.1 for discussion). In addition to these studies, a randomized, double-blind, placebo-controlled trial, known as DOSEFLEX, has evaluated the efficacy of certolizumab pegol in maintaining a clinical response when used in combination with methotrexate in patients with active RA (Sect. 4.2.4) [27].

Across trials, where specified, patients had a mean disease duration of 6–10 years [21–23], a mean or median DAS28-ESR of 6.2–7.0 [21–23] and had previously received a mean of 1.2–1.4 DMARDs other than methotrexate [22, 23]. Additional data for RAPID-1 and -2 are available in separate publications [48–50].

4.2.1 *Clinical Outcomes*

In adults with moderate to severe active RA despite prior treatment with methotrexate, adding certolizumab pegol to the methotrexate regimen significantly improved the clinical signs and symptoms of RA. Compared with placebo plus methotrexate, certolizumab pegol plus methotrexate was associated with significantly higher ACR20 response rates after 24 weeks' treatment irrespective of the maintenance dosage (200 or 400 mg q2w [22, 23] or 400 mg q4w [21]) [primary endpoint; Fig. 2]. Each certolizumab pegol regimen provided significant ($p < 0.05$) benefit over placebo in terms of this parameter from as early as week 1 [21–23], which was sustained through to week 52 in the longest trial (RAPID-1) [22].

Similarly, significantly higher ACR50 and ACR70 response rates were generally seen with certolizumab pegol plus methotrexate than with placebo plus methotrexate at 24 weeks (Fig. 2) [21–23], with maintenance of this benefit at 52 weeks in RAPID-1 [22]. In this study, a major clinical response (i.e. an ACR70 response over a continuous 6-month period) was achieved by 13 % of patients receiving certolizumab pegol and 1 % of placebo recipients [11]. In addition, across the three trials, individual components of the ACR response were significantly ($p \leq 0.05$, where specified) improved within 1–4 weeks of treatment with certolizumab pegol plus methotrexate relative to placebo plus methotrexate, with these measures remaining significantly ($p < 0.001$, where reported) improved in certolizumab pegol recipients at 12 or 24 weeks [21–23] as well as at 52 weeks [22].

Certolizumab pegol (200 or 400 mg q2w [22, 23] or 400 mg q4w [21]) plus methotrexate also reduced RA disease activity, as measured by DAS28-ESR, with recipients achieving significant ($p \leq 0.001$) mean reductions in DAS28-ESR relative to placebo plus methotrexate

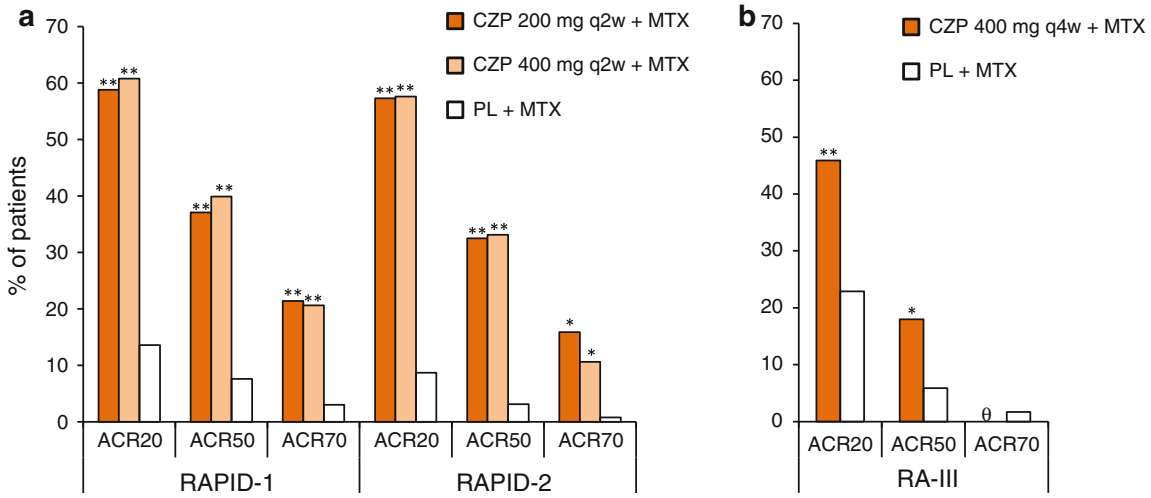

Fig. 2 Clinical efficacy of subcutaneous certolizumab pegol plus methotrexate in adults with moderate to severe active rheumatoid arthritis despite prior methotrexate therapy. Proportion of patients who, after 24 weeks' treatment, achieved a 20 % (primary endpoint), 50 % or 70 % improvement from baseline in rheumatoid arthritis signs and symptoms (as per American College of Rheumatology criteria) in three 24- [21, 23] or 52- [22] week, randomized, double-blind, trials: **a** RAPID-1 [22] and -2 [23] and **b** RA-III [21]. Patients received certolizumab pegol 200 mg ($n = 393$ [22] or 246 [23]) or 400 mg ($n = 390$ [22] or 246 [23]) every 2 weeks (preceded by a 400 mg loading dose at week 0, 2 and 4) or placebo ($n = 199$ [22] or 127 [23]) plus methotrexate in RAPID-1 [22] and -2 [23] and certolizumab pegol 400 mg every 4 weeks (without a prior loading dose) [$n = 124$] or placebo ($n = 119$) plus methotrexate in RA-III [21]. Data are for the intent-to-treat [22, 23] or modified intent-to-treat [21] population; methotrexate dosage was stable (≥10 mg/week). *ACR20, 50 and 70* 20 %, 50 % and 70 % improvement in American College of Rheumatology criteria, *CZP* certolizumab pegol, *MTX* methotrexate, *PL* placebo, *qxw* every x weeks; $*p \leq 0.01$, $**p \leq 0.001$ versus PL + MTX; θ 0 % response rate

recipients at all timepoints from week 1 onwards. Up to 12-fold more certolizumab pegol (200 or 400 mg q2w [23] or 400 mg q4w [21]) than placebo recipients were in remission (DAS28 <2.6) at 24 weeks in the two trials that reported this outcome (9.4 and 8.5 vs. 0.8 % [$p \leq 0.05$] [23]; 9.3 vs. 3.1 % [21]).

The clinical efficacy of certolizumab pegol may be more limited if antibodies against the drug develop, as ACR20 response rates were up to 1.7-fold lower in certolizumab pegol 200 mg q2w recipients who were positive for antibodies against the drug than in those who tested negative (48 vs. 60 % in RAPID-1; 35 vs. 59 % in RAPID-2) [11].

The longer-term clinical efficacy of certolizumab pegol plus methotrexate has been demonstrated in open-label extensions of RAPID-1 [51] and -2 [35]. Among patients who received certolizumab pegol 200 or 400 mg q2w plus methotrexate for the full duration of RAPID-1 or -2 (i.e. 52 or 24 weeks), treatment with certolizumab pegol 400 mg q2w plus methotrexate for a further 48 or 124 weeks sustained ACR responses ($n = 508$ [51] and 342 [35]). Moreover, ≈29 % of certolizumab pegol recipients were in remission at 100 weeks in the RAPID-1 extension (vs. ≈24.4 % at 52 weeks) [51].

Among patients who entered the RAPID-1 extension who had either moderate to severe disease activity after completing 52 weeks' treatment with certolizumab pegol 200 mg q2w plus methotrexate ($n = 118$) or had withdrawn from RAPID-1 because of inadequate response after receiving this regimen for 16 weeks ($n = 91$), increasing the certolizumab pegol dosage to 400 mg q2w for the extension was not beneficial [52].

However, some patients who were withdrawn from RAPID-1 at week 16 because of inadequate response achieved a response to certolizumab pegol 400 mg q2w plus methotrexate in the extension, with ACR20 response rates of 54 % and 63 % reached in those who had received a certolizumab pegol 400 mg q2w or placebo regimen in the initial trial ($n = 74$ and 137 entered extension) [37]. Moreover, patients who received placebo plus methotrexate during RAPID-1 and switched to certolizumab pegol 400 mg q2w plus methotrexate for the extension ($n = 41$) experienced improvements in disease activity 48 weeks after switching [51].

Post hoc analyses [53, 54] of RAPID-1 suggest that clinical responses to certolizumab pegol plus methotrexate that are more rapid and of greater magnitude may be predictive of more favourable outcomes in the longer term, with the probability of achieving low disease activity at 1 year being low if a DAS28 improvement of ≥1.2 has not occurred during the first 12 weeks of therapy.

4.2.2 Radiographic Outcomes

Certolizumab pegol plus methotrexate was effective in slowing the radiographic progression of structural damage associated with RA in the RAPID-1 [22] and -2 [23] trials.

Changes from baseline in mTSS were significantly more favourable with certolizumab pegol 200 or 400 mg q2w plus methotrexate than with placebo plus methotrexate after 24 weeks of treatment in both studies, and at 52 weeks (coprimary endpoint) in RAPID-1 (Table 2). Likewise, changes in other radiographic measures, including erosion and joint narrowing scores, also significantly favoured certolizumab pegol over placebo regimens (Table 2) [22, 23]. Similar radiographic benefit was also seen with certolizumab pegol plus methotrexate in Japanese patients with RA in another placebo-controlled trial (see Sect. 4.3) [29].

Of note, when the radiographs of patients who withdrew from RAPID-1 [22] or -2 [23] at week 16 because of inadequate clinical response were evaluated, significantly ($p \leq 0.05$) less joint damage progression was observed in those who had been receiving certolizumab pegol ($n = 150$ and 95) than in those who had been receiving placebo ($n = 120$ and 101), indicating radiographic and clinical response may not always be associated.

Certolizumab pegol plus methotrexate continued to inhibit radiographic progression of joint damage in the longer term, according to data from the open-label extensions of RAPID-1 [51] and -2 [35]. After a total of ≈2 [51] or 2.5 [35] years of therapy (last X-ray assessment [35]), the mean change from baseline in mTSS was 0.69–0.85 in patients who had received certolizumab pegol 200 or 400 mg q2w for the full duration of the initial studies (i.e. 52 or 24 weeks) followed by treatment with 400 mg q2w during the extensions. In addition, among the 11 patients who experienced radiographic progression while receiving placebo plus methotrexate for 52 weeks in RAPID-1, progression was no longer evident in five patients and was lessened in the other six patients after switching to certolizumab pegol 400 mg q2w plus methotrexate for 48 weeks in the extension [51].

4.2.3 Health-Related Quality of Life and Other Outcomes

HR-QOL generally improved with the use of certolizumab pegol plus methotrexate in the RAPID-1 [48], RAPID-2 [49] and RA-III [21] trials. Significant ($p \leq 0.05$) improvements in the eight domain scores, as well as the MCS and PCS scores, of the SF-36 were generally seen with certolizumab pegol (200 or 400 mg q2w [48, 49] or 400 mg q4w [21]) plus methotrexate relative to placebo plus methotrexate after 24 [21, 49] or 52 [48] weeks of therapy. Moreover, where specified, significantly ($p < 0.05$) more certolizumab pegol than placebo recipients had minimum clinically important differences in all SF-36 scores at weeks 24 [48, 49] and 52 [48] and several SF-36 scores at week 12 (first post-baseline assessment) [48] according to post hoc analyses.

Certolizumab pegol plus methotrexate was also effective in improving physical function, arthritis pain and fatigue,

Table 2 Inhibition of radiographic progression with subcutaneous certolizumab pegol combination therapy in double-blind trials in adults with active rheumatoid arthritis despite prior methotrexate therapy

Study	Treatment [mg q2w][a] (no. of pts)[b]	Week of eval	Mean change[c] from BL[d]		
			mTSS	JSN	ES
Keystone et al. [22] (RAPID-1)[e]	CZP 200 + MTX (393)	24	0.2**	0.2*	0.1**
	CZP 400 + MTX (390)	24	0.2**	0.2*	0.1**
	PL + MTX (199)	24	1.3	0.7	0.7
	CZP 200 + MTX (393)	52	0.4**[f]	0.4*	0.2**
	CZP 400 + MTX (390)	52	0.2**[f]	0.2*	0.0**
	PL + MTX (199)	52	2.8[f]	1.4	1.5
Smolen et al. [23] (RAPID-2)	CZP 200 + MTX (246)	24	0.2*	0.1*	0.1*
	CZP 400 + MTX (246)	24	−0.4**	−0.1*	−0.3**
	PL + MTX (127)	24	1.2	0.5	0.7

BL baseline, *CZP* certolizumab pegol, *ES* erosion score, *eval* evaluation, *JSN* joint space narrowing, *mTSS* van der Heijde modified total Sharp score, *MTX* methotrexate, *PL* placebo, *pts* patients, *q2w* every 2 weeks

* $p \leq 0.01$, ** $p < 0.001$ versus PL + MTX

[a] Maintenance dosages; CZP groups received a preceding loading dose of CZP 400 mg at weeks 0, 2 and 4

[b] Intent-to-treat population

[c] Negative changes indicate improvement

[d] Where reported [23], mean mTSS, JSN and ES scores at BL were 39.6, 20.6 and 19.0, respectively, in the CZP 200 mg q2w arm, 46.7, 25.1 and 21.6 in the CZP 400 mg q2w arm and 46.5, 23.4 and 23.1 in the PL arm

[e] All values, except mTSS at week 52, are estimated from graphs

[f] Coprimary endpoint

as measured by the HAQ-DI, VAS and FAS, respectively, in all three of these trials [21, 48, 49]. Significant ($p \leq 0.01$) improvements in HAQ-DI and VAS scores were seen with certolizumab pegol plus methotrexate relative to placebo plus methotrexate after 1 week of treatment and were sustained over 24 [21, 48, 49] and 52 [48] weeks of therapy; similar findings were reported for FAS [48, 49]. Furthermore, post hoc analyses indicated that significantly ($p \leq 0.001$) more certolizumab pegol than placebo recipients had clinically meaningful improvements in these measures at week 24 [49] and 52 [48] and from as early as week 1 [48, 49] or week 2 (in the case of physical function in RAPID-2; p-value not reported) [23].

Certolizumab pegol plus methotrexate improved workplace and home productivity, as measured by the WPS-RA [50]. Among patients working outside the home, certolizumab pegol 200 or 400 mg q2w plus methotrexate significantly ($p \leq 0.05$) reduced RA-associated absenteeism (number of work days per month missed), presenteeism (number of days per month with ≥50 % reduced work productivity) and work productivity interference compared with placebo plus methotrexate after 24 and 52 weeks of treatment in RAPID-1 ($n = 370$ evaluable). Significant ($p \leq 0.05$) reductions in presenteeism and work productivity interference (but not absenteeism) were also seen after 24 weeks' treatment with each of these certolizumab pegol plus methotrexate dosage regimens relative to placebo plus methotrexate in RAPID-2 ($n = 245$). Similar findings were generally reported for WPS-RA measures of household productivity (e.g. number of household work days missed per month and number of days per month with a ≥50 % reduction in household productivity) and participation in daily activities (number of days of family/social/leisure activities lost per month) [50].

The improvements in work and home productivity seen with certolizumab pegol plus methotrexate appeared to be associated with clinically meaningful improvements in physical function, fatigue and pain in a pooled analysis [55] of RAPID-1 and -2. Moreover, pooled data from the certolizumab pegol plus methotrexate groups of RAPID-1 indicated that improvements in home productivity may be better in those who have a clinical response to treatment earlier (i.e. at week 6) rather than later (i.e. at week 12) [38].

Longer term, certolizumab pegol plus methotrexate continued to provide benefit in measures of physical function, pain, fatigue and HR-QOL, according to the extension of the RAPID-1 trial [36, 51]. Among patients who received certolizumab pegol 200 or 400 mg q2w plus methotrexate for the full 52 weeks of RAPID-1, a further 48 weeks' treatment with certolizumab pegol 400 mg q2w plus methotrexate in the extension sustained improvements in HAQ-DI [36, 51], VAS [36], FAS [36] and SF-36 PCS and MCS [36] scores, on average above the thresholds for meaningful improvement [36]. These findings are supported in part by data from the RAPID-2 extension, in which improvements from baseline in HAQ-DI and VAS scores were sustained over 148 weeks' therapy in patients who completed 24 weeks of treatment with certolizumab pegol 200 or 400 mg q2w plus methotrexate in the initial trial and then received certolizumab pegol 400 mg q2w plus methotrexate for a further 124 weeks [35].

4.2.4 DOSEFLEX Trial

The objective of the DOSEFLEX trial was to compare the efficacy of the two recommended certolizumab pegol dosage regimens, 200 mg q2w and 400 mg q4w, in maintaining response when used in combination with methotrexate in patients with active RA [27]. The first 16 weeks of the study comprised an open-label run-in phase, during which all patients ($n = 333$) received certolizumab pegol (400 mg at 0, 2 and 4 weeks, followed by 200 mg q2w) plus methotrexate. Of those who achieved an ACR20 response at 16 weeks (i.e. responders), 209 were randomized at week 18 to receive double-blind treatment with certolizumab pegol 200 mg q2w or 400 mg q4w or placebo, in combination with methotrexate, for a further 16 weeks. In these respective groups, 61.4 %, 55.7 % and 42.0 % of patients had previously received anti-TNF therapy; patients who had previously had a primary non-response to anti-TNF therapy were excluded [39]. Statistical analyses between the certolizumab pegol groups were not reported.

Certolizumab pegol plus methotrexate was effective in maintaining clinical response in this trial, with significantly more week 16 responders sustaining an ACR20 response to week 34 (primary endpoint) with each of the certolizumab pegol plus methotrexate regimens than with placebo plus methotrexate (Table 3) [27]. Similar findings were generally observed for ACR50 and ACR70 responses (Table 3). Moreover, rates of remission (as assessed by varying criteria) were up to threefold higher in recipients of certolizumab pegol 200 mg q2w and up to fivefold higher in recipients of certolizumab pegol 400 mg q4w than in placebo recipients, with significance versus the placebo group being observed for DAS28-ESR remission (both certolizumab pegol regimens) and simplified disease activity index remission (certolizumab pegol 400 mg q4w) (Table 3) [27].

Further analysis [39] indicated that certolizumab pegol plus methotrexate sustained ACR20 responses in over half of recipients, irrespective of their prior anti-TNF therapy use. Rates of ACR20 response among certolizumab pegol 200 mg q2w, certolizumab pegol 400 mg q4w or placebo recipients at 34 weeks were 74.4 %, 61.5 % and 37.9 %,

Table 3 Efficacy of subcutaneous certolizumab pegol plus methotrexate in maintaining clinical response in patients with active rheumatoid arthritis. Results at the end of the 16-week, double-blind phase of the DOSEFLEX trial (available as an abstract) [27]

Treatment [mg] (no. of eval pts[b])	Response rate (% of pts)			Remission[a] rate (% of pts) as per		
	ACR20[c]	ACR50	ACR70	DAS28-ESR	SDAI	CDAI
CZP 200 q2w + MTX (70)	67.1*	50.0*	30.0	18.6*	17.1	21.4
CZP 400 q4w + MTX (70)	65.2*	52.2*	37.7*	29.0*	29.0*	27.5
PL + MTX (69)	44.9	30.4	15.9	5.8	13.0	15.9

ACR20, 50, 70 20 %, 50 % and 70 % improvement in American College of Rheumatology criteria, *CDAI* clinical disease activity index, *CZP* certolizumab pegol, *DAS28-ESR* 28-joint disease activity index based on erythrocyte sedimentation rate, *eval* evaluable, *MTX* methotrexate, *PL* placebo, *pts* patients, *qxw* every x weeks, *SDAI* simplified disease activity index

* $p < 0.05$ versus PL group

[a] Definitions of remission were not reported

[b] Only pts who had responded to CZP therapy in the preceding open-label phase were included (see text for details)

[c] Primary endpoint

respectively, in those with prior exposure to anti-TNF agents and 55.6 %, 70.0 % and 50.0 % among those who were anti-TNF agent naive. Similar findings were reported for ACR50 and ACR70 responses (quantitative data for the latter measure were not reported). However, among patients who had achieved an ACR20 response with certolizumab pegol in the run-in phase and were switched to placebo for the double-blind phase, clinical response appeared to be better maintained among those who were anti-TNF therapy naive.

4.3 In Asian Patients

The efficacy of certolizumab pegol, with [28, 29] or without [30] concomitant methotrexate, in treating Asian patients with active RA has been evaluated in three randomized, double-blind, placebo-controlled trials of 24 weeks' duration, two of which are known as J-RAPID [29] and HIKARI [30] (see Table 4 for details). Patients included in these studies were Japanese [29, 30] or Korean [28], had had RA for 5.4–6.2 years [28–30], and had previously had an inadequate response to [28, 29], or could not be treated with [30], methotrexate. Patients who were nonresponsive (i.e. had not achieved an ACR20 response) at weeks 12 and 14 were withdrawn from the trials (at week 16, where specified [29, 30]), and in two of the studies [29, 30], nonresponders, as well as patients who completed the trials, were eligible to participate in open-label extension studies (data not yet available).

Certolizumab pegol, with [28, 29] or without [30] methotrexate, was effective in improving the signs and symptoms of RA in these patients. Regardless of the maintenance dosage (100, 200 or 400 mg q2w), significantly more patients who received certolizumab pegol, with or without methotrexate, achieved an ACR20 response at weeks 12 and 24 than patients in the corresponding placebo groups (Table 4), with certolizumab pegol recipients experiencing significant ($p = 0.013$, where reported [28]) benefit versus placebo recipients in terms of this measure from week 1 of treatment onwards. Similar findings were observed for ACR50 and ACR70 response rates [28–30], and significantly [30] or numerically [29] more patients in the certolizumab pegol than in the placebo groups achieved RA remission after 12 and 24 weeks of treatment (Table 4).

Radiographic progression of structural damage was also inhibited with some of these certolizumab pegol regimens. Compared with the corresponding placebo group, mean increases from baseline in mTSS (indicating damage progression) after 24 weeks of therapy were significantly ($p < 0.01$) smaller with certolizumab pegol 200 or 400 mg q2w plus methotrexate (0.21 and 0.65 vs. 2.78 with placebo plus methotrexate) [29] and with certolizumab pegol 200 mg q2w without methotrexate (0.48 vs. 2.45 with placebo) [30]. Furthermore, significantly ($p < 0.01$) more patients in these certolizumab pegol groups were mTSS nonprogressors (i.e. had an mTSS change from baseline of ≤ 0.5) than in the corresponding placebo groups at this timepoint (74.1 and 70.2 vs. 47.4 % [29]; 76.3 vs. 45.6 % [30]). However, certolizumab pegol 100 mg q2w plus methotrexate did not significantly differ from placebo plus methotrexate for either of these outcomes [29]. Given these findings and the fact that certolizumab pegol 400 mg q2w appeared to provide no marked additional benefit over certolizumab pegol 200 mg q2w in terms of clinical or radiographic outcomes, 200 mg q2w was considered the optimal maintenance dosage for Asian patients [29], similar to in the EU and US (Sect. 6).

Data from subgroup analyses (some specified as post hoc) of the trial conducted in patients unable to be treated with methotrexate [30] suggested that certolizumab pegol may improve the clinical signs and symptoms of RA as

Table 4 Clinical efficacy of subcutaneous certolizumab pegol in Asian patients with active rheumatoid arthritis. Results of three double-blind trials in patients who had previously had an inadequate response to [28, 29], or could not be treated with [30], methotrexate

Study[a]	Treatment [mg] (no. of pts)	Week of eval	Response rate (% of pts)			Remission[b] rate (% of pts)
			ACR20[c]	ACR50	ACR70	
With MTX						
Kang et al. [28]	CZP 200 q2w[d] + MTX (81)	24	66.7***	43.2*	17.3*	
	PL + MTX (40)	24	27.5	20	2.5	
Yamamoto et al. [29] (J-RAPID)	CZP 100 q2w[d] + MTX (72)	12/24	62.5***/61.1***	34.7***/44.4***	13.9[e]/26.4***	8.3[e]/20.8[e]
	CZP 200 q2w[d] + MTX (82)	12/24	76.8***/73.2***	41.5***/54.9***	20.7[e]/29.3***	16.0[e]/17.1[e]
	CZP 400 q2w[d] + MTX (85)	12/24	77.6***/71.8***	51.8***/54.1***	25.9[e]/30.6***	11.8[e]/25.9[e]
	PL + MTX (77)	12/24	28.6/24.7	7.8/16.9	0.0/1.3	0.0/0.0
Without MTX						
Yamamoto et al. [30] (HIKARI)	CZP 200 q2w[d] (116)	12/24	67.2***/63.8***	37.9***/46.6***	19.0[e]/25.9***	13.8**/16.4**
	PL (114)	12/24	14.9/11.4	6.1/6.1	0.0/0.9	0.9/0.9

ACR20, 50, 70 20 %, 50 % and 70 % improvement in American College of Rheumatology criteria, *CZP* certolizumab pegol, *eval* evaluation, *MTX* methotrexate, *PL* placebo, *pts* patients, *q2w* every 2 weeks

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ vs. PL ± MTX

[a] All studies are available only as abstracts

[b] Evaluated using 28-joint Disease Activity Score based on erythrocyte sedimentation rate (no further details reported)

[c] Primary endpoint was the ACR20 response at week 12 [29, 30] or 24 [28]

[d] Maintenance dosage following induction doses of 200 mg (in 100 mg q2w group) or 400 mg (in 200 or 400 mg q2w groups) at week 0, 2 and 4

[e] P-value for the difference versus PL group was not calculated

well as inhibit radiographic progression, regardless of whether it is used as monotherapy or in combination with other DMARDs.

All certolizumab pegol-based regimens assessed in the J-RAPID [40] and HIKARI [41] trials were effective in improving physical function and pain, as indicated by significant ($p < 0.01$) reductions in HAQ-DI and VAS scores at week 24 of therapy (and as early as week 1) compared with the corresponding placebo regimens. Most certolizumab pegol regimens also significantly ($p < 0.01$ where reported) improved HR-QOL, as measured by SF-36 PCS and MCS, at both weeks 12 and 24 compared with the corresponding placebo regimen [40, 41], with the exception being certolizumab pegol 100 mg q2w plus methotrexate, which significantly ($p < 0.01$) improved only PCS (at week 24) [40].

4.4 Other Studies

4.4.1 CERTAIN Trial

A placebo-controlled, multicentre study, known as CERTAIN (CERTolizumab pegol in the treatment of RA: remission INduction and maintenance in patients with low disease activity), has compared the efficacy of adding certolizumab pegol or placebo to existing therapy in adults with low to moderately active RA responding incompletely to nonbiological DMARDs (see Table 5 for details) [32, 56]. Patients had to have received nonbiological DMARDs for the last 0.5–10 years and were excluded if they had previously been treated with biological DMARDs. At baseline, patients had a mean disease duration of ≈4.6 years and most (>90 %) had moderate disease activity (CDAI >10–22). After the initial 24-week double-blind phase of the trial, the certolizumab pegol and placebo recipients who had achieved disease remission (CDAI ≤2.8) at both 20 and 24 weeks discontinued study drug and were followed until week 52 whilst continuing their existing DMARD regimen.

In this trial, adding certolizumab pegol to an existing nonbiological DMARD regimen was associated with significantly higher rates of remission than the addition of placebo, as assessed by CDAI and other criteria, at both weeks 20 and 24 of therapy (Table 5) [32]. Moreover, the certolizumab pegol group had a twofold higher rate of remission/low disease activity (63.1 vs. 30.4 %; $p < 0.001$) and a twofold lower rate of moderate/high disease activity (37.0 vs. 69.6 %) than the placebo group at 24 weeks, indicating that certolizumab pegol may inhibit progression to high disease activity in this patient population.

Table 5 Efficacy of certolizumab pegol in adults with low to moderately active rheumatoid arthritis. Proportion of patients in remission at both 20 and 24 weeks of the double-blind CERTAIN trial [32]

Treatment [mg] (no. of randomized pts)	Remission rate[a] (% of pts) as per		
	CDAI	SDAI	DAS28
CZP 200 q2w[b] + ET (96)	18.8*	14.6*	19.8**
PL + ET (98)	7.1	4.1	3.1

CDAI clinical disease activity index, *CZP* certolizumab pegol, *DAS28* 28-joint disease activity index, *ET* existing therapy, *PL* placebo, *pts* patients, *q2w* every 2 weeks, *SDAI* simplified disease activity index

* $p < 0.05$, ** $p < 0.01$ versus PL group

[a] Only CDAI remission (primary endpoint) was defined (CDAI $\leq$2.8); all data are from an abstract

[b] Maintenance dosage following induction dose of 400 mg at week 0, 2 and 4

Although patients had low mean tender (3.8) and swollen (3.3) joint counts at baseline, those treated with certolizumab pegol had significantly ($p < 0.05$) higher ACR20 (36.5 vs. 16.3 %) and ACR50 (20.8 vs. 8.2 %) response rates than placebo recipients, although the proportion of patients achieving an ACR70 response did not significantly differ between the treatment groups (9.4 vs. 3.1 %) [32].

4.4.2 REALISTIC Trial

The efficacy of certolizumab pegol has been evaluated in a diverse group of patients with active RA, more closely representing patients seen in clinical practice, in a placebo-controlled, multicentre trial known as REALISTIC (RA EvALuation In Subjects receiving TNF Inhibitor Certolizumab pegol) [31]. Eligible patients were adults with an inadequate response or intolerance to one or more nonbiological DMARDs previously. Patients who had received prior treatment with rituximab, abatacept or three or more anti-TNF agents were among those excluded, as were patients who had received biological DMARDs within the last 1–2 months. Patients participating in the study had a mean disease duration of 8.8 years, mean swollen and tender joint counts of 11.5 and 14.7, a mean DAS28-CRP of 5.7 and received a wide variety of prior and current medications. Most patients were receiving methotrexate at baseline (69 %) and used concomitant DMARDs, such as methotrexate, leflunomide, sulfasalazine and hydroxychloroquine, at screening or throughout the study (81 %), and over one third of patients (37.6 %) had previously received anti-TNF agents, including adalimumab, etanercept and infliximab.

The trial consisted of a 12-week, randomized, double-blind phase during which patients received certolizumab pegol (400 mg at 0, 2 and 4 weeks, followed by 200 mg q2w thereafter) [$n = 851$] or placebo ($n = 212$) in combination with their current RA therapy (if any), followed by an open-label extension phase during which patients who had completed the double-blind phase could receive certolizumab pegol 200 mg q2w for a further $\geq$16 weeks ($n = 771$ and 184 entered) [31]. Efficacy was assessed in the intent-to-treat population.

Use of certolizumab pegol in this patient population was effective in improving the signs and symptoms of RA. Significantly ($p < 0.001$) more certolizumab pegol than placebo recipients achieved an ACR20 response after 12 weeks of treatment (51.1 vs. 25.9 %) [primary endpoint], with the drug providing significant ($p < 0.05$) benefit over placebo from week 2 onwards and regardless of disease duration (<2 or $\geq$2 years), baseline methotrexate use or prior anti-TNF agent use [31]. For example, the ACR20 response rate was 47.2 % with certolizumab pegol versus 27.5 % with placebo in patients with prior anti-TNF agent use ($p < 0.01$) and 53.5 % versus 25.0 % in anti-TNF agent-naive patients ($p < 0.001$).

Similar findings were reported for ACR50 and ACR70 response rates, which were significantly ($p \leq 0.002$) higher with certolizumab pegol than with placebo at 12 weeks (26.6 vs. 9.9 % and 12.9 vs. 2.8 %, respectively) and from week 2 or 6 onwards. Moreover, each individual component of the ACR response was significantly ($p < 0.001$ vs. placebo) improved with certolizumab pegol at each timepoint evaluated (i.e. weeks 2, 6 and 12) [31].

Certolizumab pegol also reduced ($p < 0.001$) disease activity, as measured by DAS28-CRP, relative to placebo after 12 weeks' therapy and almost threefold more certolizumab pegol than placebo recipients achieved disease remission (DAS28 <2.6) at this timepoint (16.0 vs. 5.7 %) [31].

In addition, there were significant ($p < 0.05$) improvements in measures of physical function (HAD-QI) [31], fatigue (FAS) [42], pain (VAS) [31] and sleep problems (Sleep Problem Index II domain and Medical Outcomes Study sleep scale) [42] with certolizumab pegol versus placebo from week 2 or 6 through to week 12 of therapy, and significantly ($p < 0.01$) more patients in the certolizumab pegol than in the placebo group achieved clinically relevant improvements in fatigue and pain at 12 weeks [42].

In the extension [43] of this trial, the clinical benefits associated with certolizumab pegol therapy at 12 weeks were maintained for a further 16 weeks of treatment in the 770 certolizumab pegol recipients who completed the initial study and continued to receive the drug during the extension (ACR20, ACR50 and ACR70 response rates were 59.7, 36.0 and 18.1 %, respectively, at 28 weeks). Clinical benefit was also observed in the 184 patients who initially received placebo and were switched to

certolizumab pegol therapy for the extension (corresponding response rates were 53.3, 31.0 and 14.7 %, respectively, 16 weeks after switching). Of note, there appeared to be a greater likelihood of achieving low disease activity with certolizumab pegol at 28 weeks among recipients whose initial clinical response was more rapid and of greater magnitude [47].

4.4.3 Observational Clinical Practice Studies

Data from two observational clinical practice studies conducted in Germany [44] and Sweden [45] have demonstrated efficacy with certolizumab pegol in patients with RA, generally supporting the findings of double-blind, placebo-controlled trials. The Swedish study ($n = 196$) analysed data from the national ARTIS (Antirheumatic Therapies in Sweden) registry and included patients for whom nonbiological DMARDs had failed, most of whom had also failed treatment with one or more biological DMARDs [45]. The German study, known as FasT, is a 104-week study for which only interim analysis data (at 12 and 52 weeks) are currently available; most patients included in the interim analysis ($n = 160$) had received prior treatment with nonbiological DMARDs (90 %) or anti-TNF agents (50 %) [44]. Patients in both studies had long-standing RA (mean duration 10.7 [44] or 11.9 [45] years) and, where reported, received certolizumab pegol 400 mg at weeks 0, 2 and 4, followed by 200 mg q2w [44].

In the Swedish study [45], certolizumab pegol therapy significantly ($p < 0.0001$) reduced RA disease activity after 3 and 6 months of treatment (mean DAS28 of 3.8 and 3.5 vs. 4.9 at baseline). Moreover, at these timepoints, most patients (>80 %) had achieved at least a moderate response (as per European League Against Rheumatism [EULAR] criteria) and ≥27 % were in remission (DAS28 <2.6).

Similar findings were reported in the German study [44]. For example, patients who completed up to 52 weeks of certolizumab pegol therapy and had no missing observations ($n = 56$ of 160 patients) experienced reductions in disease activity at 12 weeks that were sustained to the end of the 52-week period (mean changes from baseline in DAS28-CRP of −1.61 and −1.77). Moreover, 33.9 % and 44.6 % of patients were in remission and a further 28.6 % and 19.6 % had low disease activity (without remission) at these timepoints.

5 Tolerability

Tolerability data concerning the use of subcutaneous certolizumab pegol in patients with active RA are available from the clinical studies discussed in Sect. 4. This section focuses on data from the four pivotal trials that evaluated certolizumab pegol as monotherapy at a dosage of 400 mg q4w (FAST4WARD) [20] or in combination with methotrexate at a dosage of 200 or 400 mg q2w (RAPID-1 [22] and -2 [23]) or 400 mg q4w (RA-III) [21]; longer-term data from extensions of these studies are also discussed. The nature of adverse events associated with certolizumab pegol 400 mg q2w plus methotrexate was generally similar to that seen with certolizumab pegol 200 mg q2w plus methotrexate and there did not appear to be dose-related increases in the incidence of most adverse events [22, 23]; therefore, discussion of the pivotal trials is focused on the recommended certolizumab pegol maintenance dosages of 200 mg q2w or 400 mg q4w unless otherwise specified.

The findings of a recent pooled analysis (available as an abstract [57]) that included data from ten randomized trials in patients with RA (2965 certolizumab pegol and 1137 placebo recipients; 1302 and 373 patient-years exposure) and their open-label extensions (4049 certolizumab pegol recipients; 9277 patient-years exposure) are also discussed; this analysis pooled data for all certolizumab pegol dosages, including 400 mg q2w. Additional data were obtained from the EU [12] and US [11] prescribing information. In general, analyses were only descriptive.

5.1 General Profile

The tolerability profile of subcutaneous certolizumab pegol as monotherapy [20] or in combination with methotrexate [21–23] was acceptable in adults with active RA in placebo-controlled trials of 24 or 52 weeks' duration, with most adverse events being mild or moderate in intensity. Where reported, the incidence of adverse events considered to be related to study drug was broadly similar between certolizumab pegol plus methotrexate and placebo plus methotrexate in two studies [21, 22] (e.g. 55.1 vs. 54.7 per 100 patient-years in the largest trial, RAPID-1 [22]) and was 24.6 % versus 18.4 %, respectively, in another study [23].

Certolizumab pegol monotherapy was associated with 18 serious adverse events per 100 patient-years versus 9 per 100 patient-years with placebo [20]. In combination-therapy trials, the incidence of serious adverse events was 7.3 % [23] and 12.9 % [21] with certolizumab pegol plus methotrexate versus 3.2 % [23] and 10.1 % [21] with placebo plus methotrexate, with the RAPID-1 trial reporting corresponding incidence rates of 14.8 versus 12.0 per 100 patient-years [22]. Death occurred as a result of adverse events in two patients receiving certolizumab pegol plus methotrexate and one receiving placebo plus methotrexate in RAPID-1 [22] and one certolizumab pegol plus methotrexate recipient in RAPID-2 [23]; however these deaths were considered unrelated [22], or unlikely to be related [22, 23], to study drug. No deaths due to adverse events were reported in other pivotal trials when

certolizumab pegol was used in combination with methotrexate [21] or as monotherapy [20].

Withdrawal from treatment because of adverse events was relatively uncommon in these studies, occurring in 4.5 % of certolizumab pegol and 1.8 % of placebo recipients in the monotherapy trial [20] and <6 % of certolizumab pegol plus methotrexate and ≤5 % of placebo plus methotrexate recipients in combination-therapy trials [21, 23] (corresponding incidence rates in RAPID-1 [22] were 5.6 and 3.3 per 100 patient-years). Across controlled trials in patients with RA, tuberculosis (TB) infections (0.5 %), pneumonia, pyrexia, rash and urticaria (each 0.3 %) were the adverse events that most frequently resulted in discontinuation of certolizumab pegol [11].

The most common category of adverse events reported with certolizumab pegol regimens across RA trials was infections/infestations (15.5 vs. 7.6 % with placebo regimens) [12] [see also Sect. 5.2]. Bacterial and viral infections were among the adverse events considered to be at least possibly related to certolizumab pegol that occurred with an incidence of ≥1 % to <10 % in clinical and postmarketing studies in patients with RA; others included headaches, hypertension, nausea, leukopenia, eosinophilic disorders, sensory abnormalities, hepatitis, rash, pyrexia, pain, asthenia, pruritus and injection-site reactions [12]. In the pivotal clinical trials discussed in Sect. 4, the incidence of injection-site events, such as injection-site reactions and injection-site pain, was low (<5 % [20, 22, 23] or 5 events [21]) with certolizumab pegol.

The adverse event profile of certolizumab pegol was generally similar irrespective of whether it was used as monotherapy [20] or in combination with methotrexate [21–23]. Headache, nasopharyngitis, upper respiratory tract infection (URTI), diarrhoea and sinusitis were the adverse events most frequently reported (incidence ≥5 %) with certolizumab pegol monotherapy [20]. A number of these adverse events (URTI, nasopharyngitis and headache) were also among those reported most commonly with certolizumab pegol plus methotrexate in combination-therapy trials (Fig. 3) [11, 21].

The tolerability profile of certolizumab pegol therapy in patients with RA remained acceptable in the longer term, according to data from clinical trial extensions [35, 46, 51] (some of which used a dosage of 400 mg q2w) [35, 51]. For example, among patients who received continued treatment with certolizumab pegol, as monotherapy or in combination with methotrexate, for up to 7 years in an extension [46] of the 24-week FAST4WARD [20] and RA-III [21] trials ($n = 210$), adverse events and serious adverse events occurred with an incidence of 405 and 21 per 100 patient-years, respectively, and the incidence of adverse events that led to withdrawal or death was 5.7 and 0.5 per 100 patient-years. Generally similar findings were

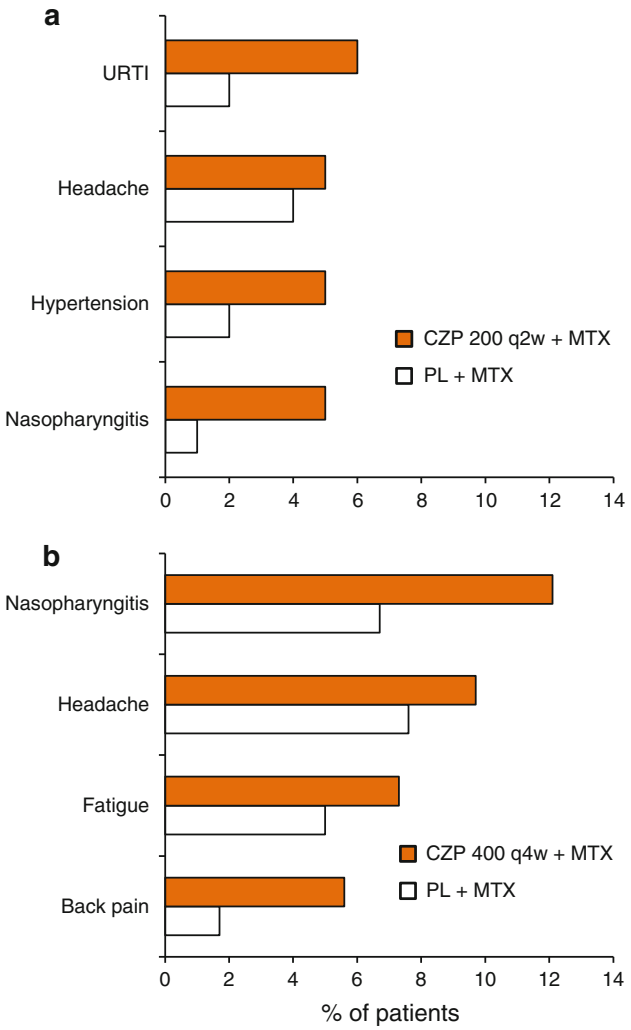

Fig. 3 Tolerability of subcutaneous certolizumab pegol therapy in patients with rheumatoid arthritis. Shown are the most frequent (incidence ≥5 %) treatment-emergent adverse events reported in **a** a pooled analysis (available from the US prescribing information [11]) of data from the randomized, double-blind trials, RAPID-1 [22] and -2 [23], in which patients received certolizumab pegol 200 mg every 2 weeks (preceded by a 400 mg loading dose at weeks 0, 2 and 4) [$n = 640$] or placebo ($n = 324$) plus methotrexate for 24 [23] or 52 [22] weeks or **b** the randomized, double-blind, RA-III trial [21] in which patients received certolizumab pegol 400 mg every 4 weeks (without a prior loading dose) [$n = 124$] or placebo ($n = 119$) plus methotrexate for 24 weeks. *CZP* certolizumab pegol, *MTX* methotrexate, *PL* placebo, *qxw* every x weeks, *URTI* upper respiratory tract infection

reported in patients who received placebo in the initial trials and were switched to certolizumab pegol therapy for the extension ($n = 192$) [46].

Indeed, no new safety signals were evident with certolizumab pegol therapy in a recent long-term pooled analysis of randomized RA trials and their open-label extensions [57]. The incidence of adverse events and serious adverse events was 336 and 21 per 100 patient-years with certolizumab pegol and 362 and 17 per 100

patient-years with placebo across the trials, and did not appear to increase with continued certolizumab pegol exposure when extension data were included (189 and 14 per 100 patient-years). Adverse events leading to death with certolizumab pegol therapy in the latter analysis occurred with an incidence of 0.63 per 100 patient-years and included cardiovascular events, malignancies, infections and other causes.

Certolizumab pegol (at recommended dosages [28–32, 43] or 100 or 400 mg q2w [29]) also had an acceptable tolerability profile in Asian patients [28–30], as well as in patients with low to moderate disease activity [32] and patients more closely reflecting those seen in clinical practice [31, 43], according to clinical trial data of up to 28 weeks duration. Where specified, no new safety signals were evident [29–31]; however, the two deaths that occurred with certolizumab pegol in one trial (due to sigmoid diverticulitis and necrotizing pneumonia) were considered possibly related to study drug [31].

5.2 Infections

Across controlled trials in patients with RA, there were 0.91 new cases of infection per patient-year with certolizumab pegol regimens compared with 0.72 per patient-year with placebo regimens; these infections were mostly of the upper or lower respiratory tract, urinary tract or were due to herpes virus [11, 12]. Serious infections (including TB, pneumonia, cellulitis and pyelonephritis) occurred with at least a threefold greater incidence with certolizumab pegol (0.06 and 0.04 per patient-year with 200 mg q2w or 400 mg q4w) than with placebo (0.02 per patient-year) in these studies [11], and were the most common serious adverse events with certolizumab pegol therapy in a recent pooled analysis (incidence per 100 patient-years of 5.61 vs. 1.35 with placebo) [57]. Notably, among 4049 patients with RA treated with certolizumab pegol, reports of opportunistic infections were uncommon (incidence 0.67 per 100 patient-years) and the incidence of TB was low (43 cases), with most TB infections occurring in central and Eastern Europe [57]; however, some TB cases have been fatal [11].

The infection profile seen with certolizumab pegol therapy in individual pivotal clinical studies discussed in Sect. 4 [20–23] is generally consistent with that discussed above. In the one trial that reported statistical analyses [21], infections occurred in significantly more certolizumab pegol plus methotrexate than placebo plus methotrexate recipients (26.6 vs. 14.3 %; $p = 0.026$), although few were serious (2.4 vs. 1.7 %). In other combination-therapy trials, the incidence of infectious adverse events with certolizumab pegol plus methotrexate and placebo plus methotrexate was 56.4 and 56.9 per 100 patient-years (RAPID-1) [22] or 27.8 % and 20.8 % (RAPID-2) [23], with those considered to be serious occurring at an incidence of 5.3 and 2.2 per 100 patient-years [22] or 3.2 % and 0 % [23]. The incidence of serious infections was also low with certolizumab pegol monotherapy (4 vs. 0 per 100 patient-years with placebo) [20].

Serious infections reported with certolizumab pegol therapy varied among these four trials [20–23]. In the largest study [22], those most frequently reported with certolizumab pegol plus methotrexate included lower respiratory tract/lung infection, urinary tract infection and TB (respective incidence rates per 100 patient-years were 1.0, 0.7 and 0.7 vs. 0 for each with placebo plus methotrexate); TB also developed in three certolizumab pegol plus methotrexate recipients in RAPID-2 [23]. The cases of TB in these two trials all occurred in patients living in Eastern Europe, where there is a high prevalence of latent TB [22, 23]; no cases of TB [20, 21] or opportunistic [20] infections were reported with certolizumab pegol therapy in the other studies. For warnings and precautions relating to serious infections, see Sect. 6.

In patients who are chronic carriers of the hepatitis B virus (HBV), certolizumab pegol, like other TNF antagonists, has been associated with reactivation of the virus; some cases of TNF antagonist-associated HBV reactivation have resulted in death [11, 12]. If HBV reactivation should occur with certolizumab pegol, the drug should be discontinued [11, 12]; in the US, caution is required if resumption of certolizumab pegol therapy is considered [11].

The risk of infection does not appear to increase with continued exposure to certolizumab pegol [11, 46, 51, 57]. For instance, in an extension [46] of two 24-week placebo-controlled trials [20, 21], patients who continued to receive treatment with certolizumab pegol, as monotherapy or in combination with methotrexate, for up to 7 years had 4.5 serious infections per 100 patient-years; similar findings were reported in patients who received placebo during the initial trials and were switched to certolizumab pegol therapy for the extension (4.3 per 100 patient-years). In these two treatment groups, TB occurred at an incidence of 0 and 0.38 per 100 patient-years, candida at 1.41 and 0.63 per 100 patient years and herpes viral infections at 5.84 and 5.25 per 100 patient-years [46]. Monitoring closely for infections is advised (Sect. 6) [11, 12].

5.3 Other Adverse Events

In clinical trials, there have been more reports of malignancies, including lymphoma, in recipients of TNF antagonists, such as certolizumab pegol, than in patients receiving placebo [12]. However, in a recent pooled analysis of RA studies, malignancies (excluding non-melanoma

of the skin) occurred with an event rate per 100 patient-years of 0.77 with certolizumab pegol versus 1.34 with placebo [57]. A total of 65 certolizumab pegol recipients in these trials and their extensions developed malignancies (event rate 0.72 per 100 patient-years), most commonly solid tumours (event rate 0.67 per 100 patient-years) [57].

Among the four pivotal 24- to 52-week trials discussed in Sect. 4 [20–23], malignant neoplasms occurred only in RAPID-1 [22] and -2 [23]. A total of eight certolizumab pegol plus methotrexate recipients (seven in RAPID-1 [2.3 per 100 patient-years] and one in RAPID-2) and two placebo plus methotrexate recipients (one in RAPID-1 [1.1 per 100 patient-years], the other in RAPID-2) reported malignant neoplasms in these studies.

Longer term, the incidence of malignancies with certolizumab pegol plus methotrexate did not appear to markedly increase over time according to the extension [51] of RAPID-1, supporting the findings of the pooled analysis discussed above [57]. There were 0.6 and 0.8 cases per 100 patient-years within 0–12 and 12–24 months of initiating certolizumab pegol therapy among the 958 patients who received either certolizumab pegol 200 or 400 mg q2w plus methotrexate or placebo plus methotrexate during the initial 52-week trial followed by certolizumab pegol 400 mg q2w plus methotrexate during the extension [51]. In the US, all patients, especially those with skin cancer risk factors, are advised to have periodic skin examinations [11].

Some certolizumab pegol recipients may develop autoantibodies. For instance, an increase from baseline in antinuclear antibody titre was observed in 17 % of certolizumab pegol recipients and 11 % of placebo recipients in the 24-week monotherapy trial [20]; however, no notable changes in autoantibody status were seen when certolizumab pegol was used in combination with methotrexate in another 24-week study [21]. Few patients with RA (<0.2 %) developed clinical signs of lupus-like syndrome with certolizumab pegol in clinical trials [11]; if symptoms of this syndrome do develop, discontinuation of certolizumab pegol is recommended [11, 12]. There have also been rare reports of neurological disorders (e.g. peripheral neuropathy, neuritis and seizure disorder) with certolizumab pegol and exacerbation/new onset of demyelinating disorders (e.g. multiple sclerosis) with TNF antagonists in general [11, 12]. However, whether long-term treatment with certolizumab pegol has any impact on autoimmune disease development is not yet known and whether a causal relationship exists between the drug and immune-related conditions remains to be determined.

New onset or worsening heart failure has occurred in patients with RA receiving certolizumab pegol therapy in placebo-controlled and open-label studies; cases usually occurred within the first year of treatment and were mild to moderate in severity [11]. In the EU, use of certolizumab pegol, like most other anti-TNF agents, requires caution in patients with mild heart failure (New York Heart Association [NYHA] class I or II) and is contraindicated in patients with heart failure that is moderate or severe (NYHA class III or IV) [12]. In the US, certolizumab pegol should be used with caution, with careful monitoring recommended, in patients with heart failure [11].

Symptoms consistent with hypersensitivity reactions (e.g. rash, angiooedema, serum sickness, dyspnoea, urticaria and hypotension), some of which were severe, have been reported with certolizumab pegol, albeit rarely; discontinuation of certolizumab pegol is recommended in the event of such reactions [11, 12].

There have been infrequent reports of haematological adverse events occurring with certolizumab pegol, including medically significant cytopenia; if significant haematological abnormalities are confirmed, discontinuation of certolizumab pegol should be considered [11, 12].

6 Dosage and Administration

Certolizumab pegol is approved for the treatment of RA in several countries, including the US [11] and those of the EU [12]. In the US [11], the drug is indicated for use as monotherapy or in combination with nonbiological DMARDs in adults with moderate to severe active RA. In the EU [12], it is indicated for use in combination with methotrexate in adults with moderate to severe active RA who have had an inadequate response to DMARDs (including methotrexate), and can be considered for use as monotherapy in patients who do not tolerate methotrexate or for whom continued use of methotrexate is inappropriate. Certolizumab pegol is not indicated for use in paediatric patients [11], with the US prescribing information carrying a boxed warning to this effect (see Sect. 7) [11], and is not recommended for use in combination with other biological DMARDs [11] (specifically anakinra or abatacept in the EU [12]), including those that inhibit TNF [11].

Certolizumab pegol is available as a reconstitutable lyophilized powder [11] or ready to use solution [11, 12] for subcutaneous injection. The recommended dosage regimen in the US [11] and EU [12] is a 400 mg loading dose administered (as two 200 mg injections) at weeks 0, 2 and 4, followed by a maintenance dosage of 200 mg q2w; 400 mg q4w may also be considered for maintenance in the US [11]. The abdomen and thigh are suitable sites for injection [11, 12].

The risk of developing serious infections (which may be fatal or require hospitalization) is increased with certolizumab pegol [11, 12], with this information featuring in a boxed warning in the US prescribing information [11].

Monitoring for signs and symptoms of infection, including TB, is recommended before [12], during [11, 12] and after [11, 12] certolizumab pegol therapy, with discontinuation of the drug if a serious infection [11, 12] or sepsis [11] develops, at least until the infection is controlled [12]. Certolizumab pegol is not recommended in patients with active infections in the US [11] and is contraindicated in patients with active TB and other severe infections in the EU [12]. All patients should be evaluated for active [12] or latent [11, 12] TB, as well as TB risk factors [11], before [11, 12] and/or during [11] treatment with certolizumab pegol.

Local prescribing information should be consulted for details regarding use in special patient populations, including patients with a history of or predisposition to infection, drug interactions, contraindications and other warnings and precautions.

7 Place of Certolizumab Pegol in the Management of Rheumatoid Arthritis

RA affects up to 1 % of adults globally [3], causing considerable joint destruction, pain and fatigue and reducing both mobility and self-care capability [58]. The overall goal of RA management is to achieve remission, although in some patients (such as those with long-standing disease refractory to therapy [59]), low/minimal disease activity may be a suitable target [6, 59–61]. To this end, it is crucial to achieve rapid control of inflammation, and starting treatment early in the course of the disease can help prevent long-term structural damage and maintain function [62].

The mainstay pharmacological option for the management of RA is DMARDs [6], which are recommended for use either as monotherapy or in combination, depending on individual patient characteristics such as disease activity and prognostic factors [6, 60, 61]. Nonbiological DMARDs have been used in RA for many years and current guidelines generally recommend initiating treatment with these agents as early as possible [6, 60], with methotrexate being preferred [6, 60] (and considered an anchor drug in combination regimens) [6, 60, 61] due to its well established efficacy and safety profile. However, although nonbiological DMARDs are generally beneficial in terms of slowing disease progression and improving the signs and symptoms of RA, they are not without their limitations [63, 64]. For instance, not all patients respond to these agents and, in some, their efficacy is lost over time [65]. Moreover, nonbiological DMARDs have a slow onset of action (often 1–6 months) and can be associated with toxicities, such as myelosuppression, anaemia and hepatotoxicity, that necessitate close monitoring [5, 64].

More recently, the treatment options available for RA were expanded considerably with the development of biological DMARDs that target the actions of proinflammatory cytokines (TNFα, IL-1, IL-6) and cells (T cells and B cells) with key roles in RA pathogenesis (Table 6) [63]. Of these agents (which include whole antibody molecules or fragments, antibody fusion proteins and cytokine receptor antagonists), those targeting TNFα were the first to be approved and are currently the biological DMARDs most commonly used to treat RA [63]. Current treatment guidelines from the ACR [61] and EULAR [6] recommend adding [6, 61] or switching to [61] an anti-TNF agent after unsuccessful treatment with either a nonbiological DMARD combination regimen [6, 61] or one [6, 61] or two [61] nonbiological DMARD monotherapy regimens, with generally similar recommendations being issued by the Canadian Rheumatology Association [60]. Other biological DMARDs (abatacept, rituximab or tocilizumab) are recommended in some of these settings as an alternative to anti-TNF agents [60, 61] or to replace anti-TNF agents in the event of inadequate response or tolerability concerns [6, 60, 61]. The guidelines also include anti-TNF agents, with [6, 60, 61] or without [61] methotrexate, as a first-line treatment option for select patients (e.g. those with early/highly active disease with features of poor prognosis).

One of the most recent anti-TNF agents to be introduced is certolizumab pegol, a recombinant PEGylated Fab′ fragment of a humanized anti-TNF antibody that neutralizes both soluble and membrane-bound TNF (Sect. 2). Unlike whole IgG molecules, which require mammalian cell expression, Fab′ fragments can be produced in microbial expression systems and are thus cheaper to manufacture, although are usually excreted more quickly [66]. However, conjugation of the PEG moiety to the Fab′ component of certolizumab increases its elimination half-life to ≈14 days (Sect. 3), allowing the drug to be administered subcutaneously q2w or q4w (Sect. 6), which may be more convenient than some other biological DMARDs that require daily (anakinra) or once/twice-weekly (etanercept and abatacept) subcutaneous administration [67–71]. Biologicals administered less frequently than certolizumab pegol q2w or q4w require intravenous infusion (e.g. infliximab [every 8 weeks] and rituximab [two separate infusions 2 weeks apart, every 16–24 weeks) [72–75]. Moreover, unlike some biological DMARDs, certolizumab pegol is not limited to use in combination with methotrexate (Table 6), allowing usage in a broader range of patients, including those who cannot receive methotrexate.

Certolizumab pegol is unique among the antibody-based biological DMARDs in that it does not contain an Fc region and consequently does not appear to be associated with the Fc-mediated effects of ADCC and CDC (Sect. 2),

Table 6 Selected comparative features of biological disease-modifying anti-rheumatic drugs currently available for the treatment of rheumatoid arthritis. Data were obtained from the most recent EU and US prescribing information and other sources [18, 63]

Agent (route of admin)	Structure	Recommended usage[a]
Targeting TNFα		
Certolizumab pegol (SC)	Fab′ fragment of humanized mAb attached to a polyethylene glycol moiety	Monotherapy or in combination with MTX[b]
Adalimumab (SC)	Human mAb	Monotherapy or in combination with MTX[b]
Golimumab (SC)	Human mAb	In combination with MTX
Infliximab (IV)	Chimeric human/mouse mAb	In combination with MTX
Etanercept (SC)	Human fusion protein of IgG Fc and TNFα receptor	Monotherapy or in combination with MTX
Targeting IL receptors		
Tocilizumab (IV)	Humanized mAb against IL-6 receptor	Monotherapy or in combination with MTX[b]
Anakinra (SC)	Antagonist of the IL-1 receptor	Monotherapy or in combination with MTX or DMARDs other than anti-TNF agents
Immune cell modulators		
Abatacept (SC or IV)	Human fusion protein of IgG Fc and cytotoxic T-lymphocyte antigen 4	Monotherapy or in combination with MTX or DMARDs other than anti-TNF agents
Rituximab (IV)	Chimeric human/mouse mAb against CD20 expressed on B cells	In combination with MTX

admin administration, *DMARD* disease-modifying anti-rheumatic drugs, *Fab′* antigen-binding fragment, *Fc* fragment crystallizable (i.e. constant) region, *IL* interleukin, *IV* intravenous, *mAb* monoclonal antibody, *MTX* methotrexate, *SC* subcutaneous, *TNF* tumour necrosis factor

[a] Some recommendations may vary slightly between the EU and US

[b] Can also be used in combination with other nonbiological DMARDs

a property that could potentially lessen the likelihood of intracellular infection [18]. In addition, in contrast to some other anti-TNF agents, certolizumab pegol does not appear to induce apoptosis of activated monocytes or PBLs or degranulation of polymorphonuclear cells (Sect. 2), although whether this has implications on its efficacy or tolerability in RA is not yet clear [18].

Monotherapy with certolizumab pegol 400 mg q4w is effective in improving the clinical signs and symptoms of moderate to severe active RA in adults for whom one or more prior DMARDs have failed, according to data from a 24-week, double-blind, placebo-controlled trial (Sect. 4.1.1). These improvements usually occurred rapidly, from as early as week 1 of treatment, and were accompanied by improvements in HR-QOL and other patient-reported outcomes, including physical function (Sect. 4.1.2). Moreover, data from patients participating in an extension of this study indicate that the clinical benefits of certolizumab pegol monotherapy are generally maintained for up to ≈2 years of treatment (Sect. 4.1.1) and that patient productivity and participation in activities may also improve (Sect. 4.1.2). Similar findings were reported after up to ≈5 years of certolizumab pegol therapy in a subsequent analysis of the extension (which also included extension participants who had previously participated in a combination therapy trial and were receiving certolizumab pegol 400 mg q4w plus methotrexate).

Generally similar benefits were seen with certolizumab pegol 400 mg q4w or 200 mg q2w when added to methotrexate in adults with moderate to severe active RA despite prior treatment with methotrexate, in three double-blind, placebo-controlled trials of up to 52 weeks' duration, with certolizumab pegol plus methotrexate also slowing radiographic disease progression (Sect. 4.2). A certolizumab pegol dosage of 400 mg q2w was also evaluated in two of these trials (RAPID-1 and -2) but, in general, did not appear to confer any marked additional benefit over the dosage of 200 mg q2w in terms of efficacy. The longer-term efficacy of certolizumab pegol plus methotrexate in this setting has been demonstrated for up to ≈3 years of treatment in extensions of RAPID-1 and -2, in which patients received certolizumab pegol at a dosage of 400 mg q2w. However, switching from the lower (200 mg q2w) to the higher (400 mg q2w) certolizumab pegol dosage for the extension was not beneficial for patients who had not already achieved low disease activity after 52 weeks' therapy or had had an early inadequate response; only certolizumab pegol dosages of 200 mg q2w or 400 mg q4w are currently recommended for use. Notably, at recommended dosages, certolizumab pegol plus methotrexate maintained clinical response in a large proportion of patients with RA, irrespective of whether they had or had not received anti-TNF therapy previously, in a well designed 34-week trial (DOSEFLEX; Sect. 4.2.4).

Additional well designed 24-week trials indicate that certolizumab pegol is effective (with or without methotrexate) in the treatment of Asian patients with RA (Sect. 4.3) and may induce remission when added to existing therapy in some patients with low to moderate disease activity incompletely responding to nonbiological DMARDs (Sect. 4.4.1), although certolizumab pegol is not currently approved for use in this setting. Certolizumab pegol also displays efficacy, regardless of baseline methotrexate use, prior anti-TNF agent use, or RA duration, in more clinically representative RA patients who have not responded adequately to one or more nonbiological DMARDs, according to data from a similarly well designed 12-week trial (REALISTIC) and its 16-week extension (Sect. 4.4.2), with these findings generally being supported by data from observational clinical practice studies (Sect. 4.4.3). Trials evaluating the use of certolizumab pegol therapy in patients with early RA who are naive to DMARDS, including methotrexate, would also be of interest, particularly as there is less potential for the findings of these studies to be confounded by patient selection criteria, such as the definition of inadequate response; such studies are planned or are currently recruiting patients [56].

The tolerability profile of certolizumab pegol in adults with RA is acceptable, regardless of whether it is used as monotherapy or combination therapy (Sect. 5). However, as biological DMARDs modulate immune responses, the risk of developing infections is increased with these agents, as with nonbiological DMARDs [8, 63]. Indeed, infections/infestations were the most common adverse events associated with certolizumab pegol therapy across RA trials (Sect. 5.1), although the risk of infection did not appear to increase with continued exposure to the drug and the incidence of TB and other serious infections was relatively low ($\leq$0.06 per patient-year; Sect. 5.2). Like other anti-TNF agents and tocilizumab, certolizumab pegol carries an FDA boxed warning relating to an increased risk of serious infections, and close monitoring for infections is advised (Sect. 6).

Biological DMARDs may also be associated with injection- or infusion-site reactions, with those occurring with intravenous agents ranging from minor to life threatening [8, 63]. The incidence of injection-site reactions and injection-site pain was low with certolizumab pegol in clinical trials (Sect. 5.1), with in vitro data suggesting that the PEG moiety of the drug inhibits mast cell degranulation, a process that releases inflammatory mediators that may cause injection-site pain (Sect. 2). As PEG moieties also reduce immunogenicity, certolizumab pegol may potentially have a lower likelihood of inducing anti-drug antibodies than agents that are chimeric monoclonal antibodies for instance [76]. Antibodies against biological DMARDs can contribute to secondary resistance, which is a considerable complication with these agents [65, 77], with antibodies against certolizumab pegol being associated with reduced clinical benefit in patients with RA in clinical trials (Sect. 4.1.1 and 4.2.1). However, patients who develop secondary resistance to one anti-TNF agent may subsequently respond to treatment with a different agent from the class [77]. Indeed, data from a small ($n < 40$), 12-week, placebo-controlled trial (available as an abstract) [78] suggest that patients with RA who are receiving nonbiological DMARDs and have discontinued anti-TNF agents due to secondary nonresponse or intolerance, may experience clinical benefit from adding certolizumab pegol to their existing therapy. Although analysis of data from larger RA trials has shown benefit with certolizumab pegol irrespective of prior anti-TNF agent use (Sect. 4.2.4 and 4.4.2), further robust trials designed specifically to evaluate the use of the drug in the setting of secondary nonresponse to anti-TNF therapy would be beneficial to confirm this finding.

Patients with RA have an increased risk of some cancers (including lymphoma, leukaemia and skin and lung cancers), although whether these arise due to rheumatoid inflammation or treatment with immunomodulating agents, such as biological DMARDs, continues to be an area of debate [79–84]. Malignancies, including lymphoma, have been reported with certolizumab pegol (Sect. 5.3), as with other anti-TNF agents [80], and owing to the occurrence of malignancies among children and adolescents receiving other anti-TNF therapies, some of which resulted in death [11], the FDA mandated that this information be included as a boxed warning for all drugs in this class [84]. Other ongoing safety concerns associated with anti-TNF agents, including certolizumab pegol (Sect. 5.3), include the potential for autoimmune diseases, demyelinating diseases and congestive heart failure [80]. Further long-term trials and clinical experience are needed to confirm or confound the potential association between anti-TNF agents and these adverse outcomes; time-to-event data may be particularly useful, given that over 60 % of lymphomas among anti-TNF agent recipients have been reported to occur in the first 4–6 months of treatment [85].

As yet, no large robust head-to-head studies have compared the efficacy and tolerability of certolizumab pegol with that of other biological DMARDs, including other anti-TNF agents, in patients with RA, although a trial comparing certolizumab pegol with adalimumab, in combination with methotrexate, is currently underway [56]. In the meantime, such treatment comparisons are limited to those made indirectly in meta-analyses [86–89] of clinical trials, although the findings of these comparisons should be interpreted with caution given their indirect nature.

Without direct comparative data, the choice of biological agent may be determined more by factors such as patient preference and convenience. Many patients appear to prefer agents that are administered subcutaneously over those that require intravenous/intramuscular administration, and prefer to be treated at home than in the hospital [90]. Most subcutaneously administered biological DMARDs, including certolizumab pegol, are available in a prefilled syringe or as a powder/solution for self-injection; etanercept, adalimumab and golimumab are also available for administration via an autoinjector pen [67, 68, 91–94], which some patients with RA-related hand deformities may find easier to use [90]. However, the certolizumab prefilled syringe has been designed to enable patients with RA to control and use it comfortably with one or both hands and has received an Arthritis Foundation ease-of-use commendation [95].

RA has a substantial economic impact [1, 3]. In addition to high direct costs, to which prescription drugs, adverse event management and hospitalizations for replacement of joints contribute considerably, RA has high indirect costs due to impairments in function and reduced productivity [58]. As pharmacoeconomic factors are likely to be important in determining treatment choices, the high cost of the biological DMARDs (e.g. average agent has yearly costs of ≈£10 000 in the UK [90]) could potentially impact on their use. Currently, cost-utility data for certolizumab pegol in patients with RA are limited to several modelled analyses conducted in various European countries from a healthcare payer perspective (available as abstracts) [96–99]. These analyses suggest that in the UK [96], Spain [97], Greece [98] and Finland [99], certolizumab pegol as monotherapy or in combination with methotrexate is generally dominant or cost effective relative to corresponding regimens of other anti-TNF agents (including adalimumab, etanercept, infliximab) or methotrexate alone. The National Institute for Health and Clinical Excellence [88] suggest that certolizumab pegol may be a cost-effective treatment option for RA in the UK if it is used as per the recommendations issued for adalimumab, etanercept and infliximab (i.e. in patients with active RA who have undergone trials of two DMARDs) [100] and is provided free of charge for the first 12 weeks of therapy via a patient access scheme.

In conclusion, subcutaneous certolizumab pegol is effective and has an acceptable tolerability profile when used as monotherapy or combination therapy in adults with active RA, including those with moderate to severe disease. Additional long-term and comparative efficacy and tolerability data are needed to position certolizumab pegol more definitively with respect to other biological DMARDs, particularly other anti-TNF agents. However, the clinical data available to date indicate that certolizumab pegol is an effective option for the management of active RA in adults.

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