Safety of Long-term Treatment With Certolizumab Pegol in Patients With Crohn's Disease, Based on a Pooled Analysis of Data From Clinical Trials

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BACKGROUND & AIMS: **Treatments for Crohn's disease (CD) have been linked to serious infections, malignancies, and dermatologic complications. We pooled and analyzed clinical trials of certolizumab pegol, a pegylated humanized Fab' fragment against tumor necrosis factor, to quantify safety events in patients with CD.**

METHODS: **We collected data from 5 placebo-controlled trials, 9 open-label studies, and 1 dose-regimen study, conducted globally through April 2014. A total of 2570 patients with moderate to severe CD were treated with certolizumab pegol, with 4378.1 patient-years of exposure. Data were analyzed in 2 groups: patients from placebo-controlled (PC) trials treated with placebo (n = 875) or certolizumab pegol (n = 919) for 6 to 38 weeks (the PC group) or all patients exposed to certolizumab pegol (n = 2570), for durations of 6 to 362 weeks (the all-studies group). Incidence rates (IRs; incidence/100 patient-years) of adverse events (AEs) were calculated from first dose through 70 days (approximately 5 half-lives) after the last dose.**

RESULTS: **In the PC group, IRs for serious AEs were similar among patients given certolizumab pegol (31.35/100 patient-years) vs placebo (24.33/100 patient-years). IRs of serious infections or malignancies were low among patients receiving short-term treatment with certolizumab pegol (8.49/100 patient-years and 1.01/100 patient-years, respectively, in the PC group) and did not increase with long-term treatment (6.47/100 patient-years and 0.80/100 patient-years, respectively, in the all-studies group). IRs of psoriasis or psoriasiform dermatitis were low in the PC group (1.01/100 patient-years and 0/100 patient-years, respectively); in the placebo group, these IRs were 0.38 per 100 patient-years and 0 per 100 patient-years, respectively. IRs of psoriasis or psoriasiform dermatitis did not increase with long-term treatment (0.93/100 patient-years and 0.09/100 patient-years, respectively, in the all-studies group).**

CONCLUSIONS: **Based on an analysis of data pooled from 15 trials of patients with CD, the safety profile for long-term therapy with certolizumab pegol therapy is similar to that reported from short-term studies. Overall rates of AEs, serious infections, malignancies, and psoriasis did not increase with long-term treatment, suggesting a favorable risk–benefit ratio with long-term certolizumab pegol therapy in CD. Clinicaltrials.gov identifiers: NCT00291668, NCT00152490, NCT00152425, NCT00308581, NCT00349752, NCT00552058, NCT00329550, NCT00329420, NCT00160524, NCT00160706, NCT00297648, NCT00333788, NCT00307931, NCT00356408, and NCT00552344 (https://www.clinicaltrials.gov/ct2/search).**

Keywords: TNF; Complication; Side Effects; Pooled Analysis.

Abbreviations used in this paper: AE, adverse event; CD, Crohn's disease; CI, confidence interval; IR, incidence rate; MedDRA, Medical Dictionary for Regulatory Activities; NMSC, nonmelanoma skin cancer; OL, open label; PC, placebo-controlled; PPD, protein-purified derivative; ROW, rest of world; SAE, serious adverse event; SMR, standardized mortality ratio; TB, tuberculosis; TNF, tumor necrosis factor; WHO, World Health Organization.

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Crohn's disease (CD) is a chronic inflammatory disease that requires long-term treatment with immunosuppressive therapy such as anti-tumor necrosis factor-α (anti-TNFα) agents. As a therapeutic class, anti-TNFα antagonists have been associated with adverse events (AEs) including serious infections,[1,2] malignancies,[3] dermatologic complications such as melanoma,[4] nonmelanoma skin cancers,[5] psoriasiform skin lesions,[6,7] demyelinating events, drug-induced lupus-like reactions, and congestive heart failure.[8,9] Opportunistic infections can be serious, but the absolute incidence is low.[9] The potential risk for lymphoproliferative diseases with anti-TNFα agents is also of interest,[10] but current data are confounded by the widespread use of immunomodulators such as azathioprine and 6-mercaptopurine.[4,11,12]

Certolizumab pegol, a subcutaneously administered recombinant, humanized, polyethylene glycol–conjugated, antigen-binding fragment (Fab') with specificity for human TNFα, is approved for the treatment of moderate to severe CD in multiple countries. The safety of certolizumab pegol during the treatment of CD has been evaluated in placebo-controlled (PC) studies and open-label (OL) studies.[13–15]

The aim of this retrospective pooled data analysis was to assess the safety of certolizumab pegol in patients with CD using data from UCB Pharma-sponsored and UCB Pharma-conducted clinical trials. These data allowed us to determine the incidence rates (IRs) of clinically important AEs, a standard method for measuring safety across studies.

Methods

Studies and Designs

Data from 15 phase 2 through 3b UCB-conducted studies of moderate to severe CD patients were pooled: 5 randomized PC studies (duration, 6–38 wk), 9 OL studies (duration, 16 wk to 7 y), and 1 randomized, dose-regimen study of certolizumab pegol (duration, 54 wk) (Supplementary Table 1).[13–22] Fourteen studies were completed; 1 OL study was ongoing at the time of these analyses (data cut-off date, April 14, 2012).

For PC studies, an induction of 400 mg certolizumab pegol or placebo subcutaneously at weeks 0, 2, and 4 was followed by certolizumab pegol or placebo maintenance administered as 400 mg every 4 weeks. Five of the OL studies followed induction regimens with certolizumab pegol; in all OL studies, maintenance certolizumab pegol was administered at 400 mg every 4 weeks, with 2 studies administering certolizumab pegol 400 mg every 2 weeks for certain patients (Supplementary Table 1).[16,17]

Study data originated from multicenter, multinational (38 countries) clinical trials for the certolizumab pegol program in CD.

Adverse Events

Treatment-emergent AEs were defined as any untoward medical event starting on or after the first dose and within 70 days or fewer (approximately 5 half-lives) after the last dose. Treatment-emergent serious AEs (SAEs) were those that led to death; were life-threatening; required in-patient hospitalization or extension of hospitalization; resulted in persistent or significant disability/incapacity, congenital anomalies, or birth defects; or required medical or surgical intervention to prevent the other criteria from occurring. Serious infections were those requiring parenteral antibiotics and/or included SAE criteria. Malignancies were identified by standard Medical Dictionary for Regulatory Activities (MedDRA) query: "malignant tumors." Dermatologic events were mapped to a high-level term of skin and subcutaneous tissue disorders. In studies before 2007, screening for tuberculosis (TB) was conducted according to the national guidelines of the recruiting center (the criteria for a positive purified protein derivative [PPD] test varied between $\geq$5 and $\geq$20 mm). In 2007, protocols were amended mandating that patients be treated prophylactically for TB if PPD positivity of 5 mm or greater was observed at baseline.[23,24] Data were probed for TB events using the standard MedDRA query: "tuberculosis infections," "Mycobacterium test positive," "Mycobacterium tuberculosis complex test positive," and "tuberculin test positive."

All AE data were mapped to MedDRA version 15.1, and the coding of AEs across studies was reviewed for consistency. Prior medications were coded using the World Health Organization (WHO) drug dictionary, June 2012.

Statistical Methods

Safety data were divided into 2 separate CD populations: the PC group (patients treated with either placebo or certolizumab pegol, allowing between-treatment comparisons); and the all-studies group (all patients with certolizumab pegol exposure, allowing safety assessment of long-term certolizumab pegol exposure). All patients who received at least 1 dose of study drug were included. The data include 2 different placebo formulations: saline and sorbitol. Certolizumab pegol data in the PC group and all-studies group included patients who received at least 1 dose of certolizumab pegol.

For IRs, the numerator was the total number of patients experiencing the AE; the denominator was the summation of individual patient-years at risk up to the first occurrence of the AE plus the total patient-years at risk for those patients not experiencing that AE, divided by 100. IRs included a 95% confidence interval (CI) based on the chi-square distribution. For event rates, the numerator was the total number of occurrences of an AE (including repeat occurrences in individual patients) divided by the total number of patient-years divided by 100.