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Compassionate use of certolizumab pegol in patients with Crohn's disease who have failed previous TNF inhibitor therapies

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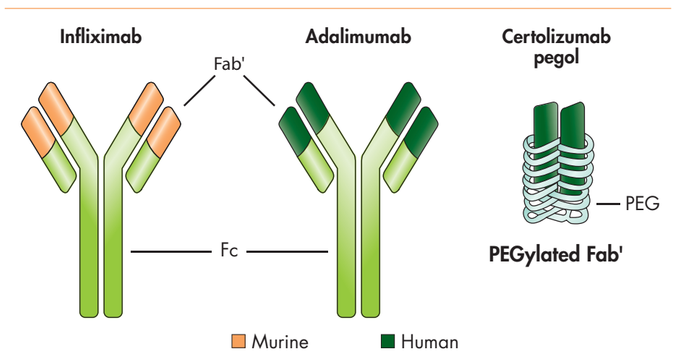
Introduction

- Patients with moderate to severe Crohn's disease whose symptoms cannot be controlled by corticosteroids or immunosuppressants have increasingly sought effective therapy with biologic agents, such as infliximab and adalimumab.
- However, even with these anti-TNF agents, a proportion of patients relapse and lose their response due to disease flare or adverse reactions, leading to cessation of therapy.
- The anti-TNF certolizumab pegol has shown favourable efficacy when used as a third-line therapy in patients with Crohn's disease who have lost response or developed intolerance to other anti-TNFs and for whom no other therapeutic options exist.[1]
- Unlike the more conventional anti-TNFs infliximab and adalimumab (which are monoclonal antibodies), certolizumab pegol is a novel PEGylated anti-TNF with features that may limit intolerance, such as absence of an Fc region and a Fab' region site-specifically linked to 40 kDa polyethylene glycol (PEG) moiety (Figure 1).

Figure 1. Comparative structures of the anti-TNF agents infliximab, adalimumab and certolizumab pegol



Adapted from: Bourne T, et al. Biodrugs 2008;22:331–337.

- To date there have been several Phase III clinical trials on certolizumab pegol that have established its safety and efficacy without the need for dose escalation in different populations: the pivotal studies PRECiSE 1 and 2 (NCT00152425 and NCT00160524)[2,3] and their associated open-label studies PRECiSE 3 and 4 (NCT00160524 and NCT00160706)[4,5]; WELCOME (NCT00308581)[6]; and MUSIC (NCT00297648).[7]
- Certolizumab pegol has been approved in the United States and Switzerland since 2008 for the treatment of adult patients with moderate to severe Crohn's disease[8] and has also been used in a compassionate-use program called COMPAS in Europe and Canada since 2006.[9]
- COMPAS is an ongoing program for patients with an unmet medical need in which physicians are permitted to use certolizumab pegol in patients with active Crohn's disease who have failed approved therapies. COMPAS was initiated by UCB, the manufacturer of certolizumab pegol.

Objective

- To describe a retrospective update of COMPAS data on the efficacy, safety and tolerability of certolizumab pegol.

Methods

Recruitment

- Physicians submit requests to UCB Global Headquarters in Brussels via the local country affiliate company for each patient deemed suitable for assessment to be included in the COMPAS program, based on their disease and treatment history (see box below for inclusion/exclusion criteria).

Therapy

- The recommended dose regimen administered to all patients in COMPAS is 400 mg subcutaneous (sc) induction at Weeks 0, 2 and 4, followed by certolizumab pegol 400 mg sc maintenance every 4 weeks (q4w). This regimen is identical to the prescribers information for the United States and Switzerland.[8]
- Treatment is deemed effective if there is a clinical response (clinical improvement satisfactory to both patient and investigator with the patient remaining on treatment) and no adverse drug reactions (ADRs) leading to withdrawal.

Data cut-off

- Recruitment and treatment data are presented up to the data cut-off date of 6 November, 2009.
- Due to the nature of the compassionate-use program, where UCB cannot collect data but relies on reports received from participating physicians, information presented here is the closest best estimate to the actual data.

Inclusion criteria

- Adult patients (aged >18 years) with active Crohn's disease despite previous therapy with steroids, azathioprine, methotrexate and anti-TNF agents (infliximab and adalimumab), or proven intolerance to these drugs.
- Positive hepatitis B and/or hepatitis C and/or HIV status ruled out.
- Adequate contraception if the patient is of childbearing potential.

Exclusion criteria

- Biologic or experimental therapy 8 weeks before inclusion.
- Hypersensitivity to certolizumab pegol or any of its excipients.
- Severe progressive renal, hepatic, hematological or gastrointestinal disease (other than Crohn's disease), endocrine, pulmonary (including active or latent tuberculosis) or cardiac disease, or neurological disorders.
- History of malignant or lymphoproliferative disease.
- Life-threatening infections within 6 months of inclusion.

Results

- By 6 November, 2009, COMPAS involved 346 gastroenterologists in 18 countries and 823 requests from physicians had been received by UCB Global Headquarters via the local affiliates, representing increases of 190% and 290%, respectively, since the last reported cut-off date of May 2007.
- Drug-release criteria were met by 779 patients, of whom 658 had received at least 1 dose of certolizumab pegol by the cut-off date, an increase in patient numbers since May 2007 of 361% and 411%, respectively (Table 1).

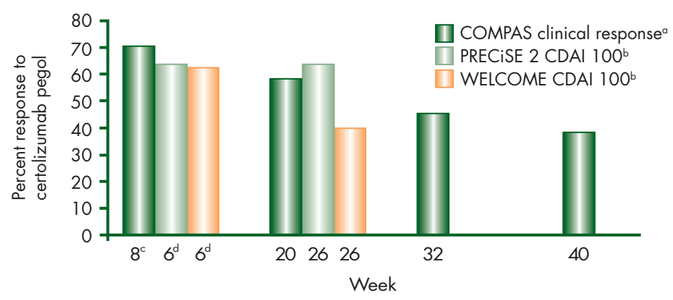
Table 1. Summary of patient recruitment into the COMPAS program and treatment across all countries as of 6 November, 2009

Status	Patients dosed (induction)	Patients reached maintenance (Week 8 or fourth dose)	Patients currently in maintenance (at or beyond Week 8 or fourth dose)	Dropouts in induction	Dropouts in maintenance	Dropouts (total)
Austria	14	14	8	0	6	6
Belgium	37	28	11	8[a]	17	25
Canada	42	35	0	7	35	42
Czech Republic	22	22	6	0	16	16
Denmark	17	17	8	0	9	9
Finland	4	4	0	0	4	4
France	159	108	25	18	83	101
Germany	93	63	30	26[a]	33	59
Greece	14	12	0	2	12	14
Ireland	11	9	5	2	4	6
Italy	32	27	5	5	22	27
The Netherlands	87	73	28	13[a]	45	58
Norway	5	3	3	2	0	2
Portugal	3	3	0	0	3	3
Spain	52	43	18	9	25	34
Sweden	23	22	10	1	12	13
Switzerland	9	2	0	7	2	9
UK	34	18	12	12[a]	6	18
Total	658	503	169	112	334	446

[a]Dropouts in induction take into account patients still in induction at cut-off date (1 for Belgium; 4 for Germany; 1 for The Netherlands; 4 for the UK).

- Most patients were receiving immunosuppressants and/or corticosteroids at baseline.
- The majority of patients had failed treatment with either infliximab or adalimumab or both at inclusion in COMPAS.
- 8 weeks after starting treatment (ie, 4 weeks after the final induction dose) 76.4% (503/658) of patients had responded to certolizumab pegol treatment (Table 1). Of these, 70.1% (461/658) were still in response by the first visit after Week 8; 58.2% (383/658) remained on treatment at Week 20, 45.1% (297/658) at Week 32 and 38.4% (253/658) at Week 40 (Figure 2).

Figure 2. Comparison between COMPAS, PRECiSE 2 and WELCOME patient response rates to treatment with certolizumab pegol



CDAI, Crohn's Disease Activity Index. [a]COMPAS clinical response defined as a clinical improvement satisfactory to both patient and clinician investigator, with the patient remaining on treatment with certolizumab pegol. [b]CDAI 100 response defined as a decrease in CDAI score of at least 100 points. [c]Week 8: 4 weeks after last induction dose. [d]Week 6: 2 weeks after last induction dose.

- By the cut-off date there had been a total of 446 dropouts (Table 1).
- These efficacy data from COMPAS compare favourably with the response to certolizumab pegol 400 mg in 2 relevant randomised clinical trials (Figure 2):
  - In PRECiSE 2[3] 64.1% (428/668) of the intention-to-treat patients responded to induction with open-label certolizumab pegol by Week 6, and by the study end (Week 26), 62.8% of the randomised certolizumab pegol group responders (135/215) remained in response
  - In WELCOME[6], the open-label induction response rate at the end of Week 6 was 62.0% (334 of 539 patients), and by study end (Week 26), 39.9% of the randomised patients in the arm receiving 400 mg q4w (67 of 168 patients) remained in response.
- Up to the 6 November, 2009, cut-off date, ADRs had been reported in 112 patients (Table 2).
- There were 70 serious ADRs (SADRs), which occurred in 42 patients.

Table 2. Summary of ADRs in COMPAS patients to 6 November, 2009

	No. of events	No. of patients
ADRs		
Total ADRs	133	75
Gastrointestinal disorders	16	16
Infections	23	18
Malignancies	0	0
SADRs		
Total SADRs	70	42
Serious gastrointestinal disorders	15	15
Serious infections	17	13
Malignancies	2	2
SADRs associated with death	6	4

- The most frequently reported SADRs were gastrointestinal disorders in 15 patients (exacerbation or new episode of Crohn's disease in 9 patients) and serious infections in 17 patients. There were no reports of tuberculosis.
- Other SADRs included:
  - Malignancies in 2 patients; small intestine carcinoma in a patient with a history of severe Crohn's disease who had received successive immunosuppressants and 5 months of therapy; fistulous carcinoma in another patient with previous therapy for Crohn's disease with infliximab and adalimumab for 3.5 years
  - Acute left cardiac insufficiency and renal failure in a patient who was obese, had a family history of myocardial infarction and had received 2 weeks of therapy
  - Acute urticaria in a patient who had experienced similar reactions to previous anti-TNF therapies.
- 4 deaths occurred (1 cardiac arrest due to myocardial infarction; 1 due to respiratory failure resulting from inhalation of gastric material; 1 due to MRSA pneumonia and acute renal failure; 1 due to multiple organ failure following surgery for fistulous carcinoma), but were judged by the reporting physician as unlikely or not to be related to treatment.

Conclusions

- COMPAS was designed for patients with moderate to severe, active Crohn's disease who meet certain criteria to receive certolizumab pegol under real-life, clinical practice conditions.
- To date, COMPAS demonstrates that certolizumab pegol q4w is effective in non-clinical-trial patients with difficult-to-treat Crohn's disease, including those who had previously failed other TNF inhibitor therapies.
- Despite inclusion of only patients with severe and resistant disease (a Crohn's disease population known to be difficult to treat), the clinical efficacy and safety profiles of certolizumab pegol to date in this ongoing study compared favourably to those observed in controlled clinical trials.

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Disclosures

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