

NEW DRUG REVIEW

Certolizumab Pegol for Moderate-to-Severe Crohn's Disease

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In September of 2005, Dr. Stefan Schreiber and colleagues published in *Gastroenterology* the first of three trials examining the efficacy of the anti-tumor necrosis factor (TNF) agent certolizumab pegol (Cimzia, UCB) for the treatment of Crohn's disease (CD). The study enrolled a total of 292 patients, who were randomized to receive induction doses of 100 mg, 200 mg, or 400 mg of certolizumab pegol or placebo at weeks 0, 4, and 8; this dose-finding trial did not employ a loading-dose strategy. The primary endpoint was response, defined as a 100-point reduction from baseline Crohn's Disease Activity Index (CDAI) score at week 12. At weeks 2 and 4, statistically significant differences in response were seen for nearly all doses when compared to placebo and for the 400 mg dose when considering the number of patients in remission. After week 4, placebo rates of response and remission rose progressively. Although the 400 mg dose maintained significant differences for the majority of time points throughout the trial, by the endpoint of 12 weeks, the placebo rate was very high and none of the doses showed significant differences. However, when considering the results of the trial as a whole, the drug was shown to have overall efficacy and the highest dose was shown to be most effective.

With this knowledge established, we were able to design and conduct the phase III PRECISE 1 and 2 trials, which were published in the *New England Journal of Medicine* in July 2007. I served as lead investigator on PRECISE 1, and Dr. Schreiber again served as lead on PRECISE 2.

The PRECISE 1 trial looked at 24 weeks of therapy in patients with moderate-to-severe CD. Patients (N=662) received 400 mg of certolizumab pegol or placebo at 0, 2, and 4 weeks and then every 4 weeks through week 24. Final treatment assessment was made at week 26. The primary endpoint was, again, a 100-point reduc-

tion in baseline CDAI. In order to capture both the induction and maintenance data, these patients were treated continuously, without rerandomization of responders at week 6. At week 6 and then at a combined endpoint of weeks 6 and 26 (coprimary end-

points), significant differences in efficacy between certolizumab pegol and placebo were demonstrated. However, some of the same placebo-rate issues seen in the first Schreiber trial were also seen in PRECISE 1. At the earlier time points, such as week 4, the response and remission rates for certolizumab pegol were significant compared to placebo, but by week 6 and some of the later time points, although trends toward higher remission rates with certolizumab pegol remained, the significant difference was lost due to rising placebo rates.

The design of PRECISE 2 was more comparable to trials of other anti-TNF drugs for CD. Patients with active disease received open-label induction therapy with 400 mg of certolizumab pegol at weeks 0, 2, and 4. At 6 weeks, patients experiencing clinical response, again defined as a 100-point reduction from baseline CDAI score, were randomized to continue certolizumab pegol or placebo every 4 weeks, through week 24, with final assessment at week 26. Among the patients responding to induction therapy, there were highly significant differences in both maintenance of response and remission in the certolizumab pegol group compared to placebo.

Based on the results of these three trials, as well as open-label extensions at the phase III stage, the US Food and Drug Administration approved certolizumab pegol in April 2008 for the induction and maintenance of clinical response in patients with moderate-to-severe CD.

Monoclonal antibodies are made up of an FC portion and an FAB portion. The FAB portion, in turn, has two arms that each bind antigens. Certolizumab pegol is termed an FAB fragment because it has no FC portion and only half of the FAB portion (one of the two antigen-binding arms) of the antibody. The molecule is humanized (approximately 95% human), which, in principle, should produce less immunogenicity. Because an FAB fragment has a relatively short half-life, certolizumab pegol is pegylated to extend its half-life to 14 days. Certolizumab pegol is administered subcutaneously, and the dose and half-life are compatible with every-4-week dosing.



Subcutaneously administered anti-TNF drugs can be associated with injection-site reactions, which have been shown to be quite low with certolizumab pegol, in the range of 1–3%. Because certolizumab pegol is not given intravenously, there are no problems with acute or delayed infusion reactions, which can be seen with the intravenous chimeric antibody infliximab. Interestingly, there is also a low rate of anti-nuclear antibody (ANA) and double-stranded DNA formation with certolizumab pegol. Double-digit rates of ANA formation have been observed with the immunoglobulin (Ig)G1 antibodies, anywhere from the high teens for adalimumab up to as much as 30–40% or more with infliximab over time. It appears that the rates are lower, in the single digits (anywhere from 2–3% to 8–9%) with certolizumab pegol. However, it is important to point out that with all of these drugs, the occurrence of drug-induced lupus is quite rare. Whether these apparent differences in the rates of ANA formation result in any meaningful differences in the rates of autoimmunity and drug-induced lupus is unclear.

IgG1 antibodies (infliximab and adalimumab) engender placental transfer in pregnant women, and there is an increase in the level of IgG1 transfer during the third trimester that leads to concentration of the antibody (drug) in the fetus. In contrast, current evidence shows that a pegylated FAB fragment does not cross the placenta. It should be noted that none of these drugs is approved for use during pregnancy. However, based on animal-model data, it would appear that certolizumab pegol would not cross the placenta and expose the fetus if taken during pregnancy.

For patients who have lost response to an anti-TNF agent, most of our experience with infliximab and adalimumab has been to increase the dose or dosing frequency to regain response and then continue with the increased regimen. In extension trials with certolizumab pegol, where patients responded but then lost response, the strategy was to reinduce with certolizumab pegol 400 mg at 0, 2, and 4 weeks and then return to every-4-week dosing at 400 mg, rather than increase the dose or shorten the dosing interval. Because the maintenance regimen with certolizumab pegol is 400 mg every 4 weeks, this strategy requires only one extra 400 mg dose between two maintenance doses. Using this reinduction strategy, approximately one third of patients who had lost response were able to regain and maintain it. It is interesting that

one third of patients will respond in this situation, simply by giving one extra dose. Conversely, a dosing strategy of 200 mg or 400 mg every 2 weeks may regain response in even more patients. Although the reinduction strategy is a useful starting point for this patient population, it may not be the only option. Sustained dose escalation or interval shortening could regain response in an even larger percentage of these patients. An overall protocol for regaining efficacy in certolizumab pegol patients with attenuated response remains to be developed.

Considered retrospectively, neither the phase II trial nor the PRECISE 1 phase III trial was optimally designed to demonstrate the full short-term induction benefit of certolizumab pegol. There is an additional induction trial currently ongoing, in which patients are dosed at 0, 2, and 4 weeks and assessed at 6 weeks for induction of response and remission, to better clarify the full range and magnitude of initial response to certolizumab pegol. There is also a trial currently recruiting to evaluate the steroid-sparing benefit of certolizumab pegol. Another ongoing trial is examining the ability of certolizumab pegol to induce and maintain endoscopic (mucosal) healing. Finally, preliminary data have been reported from the WELCOME trial, which is evaluating different certolizumab pegol dosing strategies in patients who had previously received anti-TNF therapy and who had either lost response or become intolerant. WELCOME is designed with an open-label induction phase, followed by randomization of patients who respond to maintenance therapy with different doses of certolizumab pegol. The currently reported induction data suggest that approximately 60% of patients who have previously responded to treatment with another anti-TNF, and then lost response or become intolerant, will respond to certolizumab pegol. Maintenance data are forthcoming.

Suggested Reading

Schreiber S, Khaliq-Kareemi M, Lawrance IC, Thomsen OO, Hanauer SB, et al. Maintenance therapy with certolizumab pegol for Crohn's disease. *N Engl J Med.* 2007;357:239-250.

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Schreiber S, Rutgeerts P, Fedorak RN, Khaliq-Kareemi M, Kamm MA, et al. A randomized, placebo-controlled trial of certolizumab pegol (CDP870) for treatment of Crohn's disease. *Gastroenterology.* 2005;129:807-818.