

The PRECiSE 2 trial of certolizumab pegol, a new PEGylated anti-TNF agent, in the treatment of Crohn's disease

An interview with David A Schwartz, 13 June 2007

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Context: Certolizumab pegol (CDP 870) is a new anti-tumor necrosis factor (TNF) therapy currently in development for the treatment of Crohn's disease, rheumatoid arthritis, and psoriasis. Certolizumab pegol is the first PEGylated biologic anti-TNF agent and has a high binding affinity for TNF. Dr. Schwartz was an investigator of the PRECiSE (PEGylated Antibody Fragment Evaluation in Crohn's Disease Safety and Efficacy) 2 trial of certolizumab pegol in patients with Crohn's disease.

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Q. How would you describe the role of anti-TNFs in Crohn's disease?

A. Currently, anti-tumor necrosis factors (TNFs) are reserved for the treatment of patients with moderate-to-severe Crohn's disease for whom standard therapy (with immunomodulators, for instance) has failed. The role of anti-TNF agents, however, is evolving. During the past few years we have seen the introduction of a 'top-down' treatment strategy, which involves immunomodulators and biologic agents being used earlier in the course of the disease in order to prevent some of the complications that arise with Crohn's disease. Consequently, we are starting to use anti-TNF therapy earlier for patients with Crohn's disease who have features of more aggressive disease, such as a history of surgery, fistulas, or the need for steroids at the initial presentation. Such a strategy more effectively improves quality of life and changes the natural course of the disease. For instance, in perianal Crohn's disease, an anti-TNF is now the first-line therapy for our patients. We use an anti-TNF quite frequently at first diagnosis in order to prevent some of the complications that can occur with fistulizing Crohn's disease.

Q. What do you think certolizumab pegol brings to the equation?

A. Certolizumab pegol brings a novel option for patients who are suitable candidates for anti-TNF therapy and those who may have had difficulties with the conventional anti-TNFs that are currently available. It also gives patients perhaps a more convenient option in that it only needs to be administered once monthly, as opposed to weekly or every other week with the other injectable agents available. Certolizumab pegol has an increased drug half-life as a result

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of it being PEGylated (ie, conjugated to polyethylene glycol) and this makes less frequent dosing possible. The efficacy and tolerability data of certolizumab pegol look very good and I am hopeful that it will provide a very effective treatment option for patients with Crohn's disease.

Q. Now could you describe the methodology of the PRECISE 2 clinical trial?

- A.** PRECISE 2 is a multicenter, randomized, double-blind, placebo-controlled trial. It included 668 patients with moderate-to-severe Crohn's disease. To be enrolled in this trial, patients had to have a Crohn's Disease Activity Index (CDAI) score of >220 points. Patients were given open-label certolizumab pegol 400 mg at 0, 2, and 4 weeks (induction). Those who achieved a 100-point decrease in their CDAI score were then randomized to receive either placebo every 4 weeks or certolizumab pegol 400 mg every 4 weeks (maintenance). The primary endpoint was the number of patients with a baseline C-reactive protein (CRP) concentration >10 mg/L who had a 100-point decrease in CDAI score at Week 26. Data for the certolizumab pegol group were compared with those for the placebo group.

Q. What were the main findings from the PRECISE 2 trial?

- A.** The primary endpoint was a 100-point response on the CDAI. We found that 63% of patients who received certolizumab pegol met that endpoint, compared with 36% of patients receiving placebo. Another endpoint was remission; at Week 26, 48% of patients who received certolizumab pegol were in remission compared with 29% of patients in the placebo group. For both of these endpoints, the difference was statistically significant. Interestingly, similar results were obtained in the overall population, which also included those patients who did not have a baseline CRP serum level of at least 10 mg/L.

Q. How do these results compare to those of the other anti-TNF agents?

- A.** It is hard to directly compare the results of one trial with the results of another because the trial designs are

subtly different, and different inclusion and exclusion criteria are used. That being said, the endpoints used in the different trials are very similar. In PRECISE 2 (the remission rate at Week 26 in the certolizumab pegol group was 31%. The adalimumab CHARM trial was of a similar design to PRECISE 2, including an induction phase followed by a maintenance phase) and the remission rate at Week 26 was 27% in the active treatment group. In the ACCENT 1 trial of infliximab, the remission rate in the active group was 23% at Week 30.

Q. In the PRECISE 2 trial, what was the efficacy of certolizumab pegol in patients with prior exposure to infliximab?

- A.** Many of the trials with biologic anti-TNF agents indicate that patients with previous exposure to an anti-TNF antibody treatment may have a slightly reduced response rate when treated with a second anti-TNF agent. If you look at those patients in PRECISE 2 with no prior infliximab exposure, 69% of patients who subsequently received certolizumab pegol responded, compared with only 40% of the patients who received placebo maintenance treatment. Among patients who had previously received infliximab, the corresponding values were 44% of patients receiving certolizumab pegol compared with 25% for placebo. It may be the case that, over time, the patients with prior infliximab exposure may develop strictures or other such complications that are a bit more refractory to treatment. This is possibly one explanation for the slightly lower response rate in patients who have previously received infliximab. The response rate was still statistically significantly greater with certolizumab pegol than with placebo, but slightly lower than in patients for whom certolizumab pegol was the first-line anti-TNF. This observation is not specific for certolizumab pegol (having also been seen with other anti-TNFs).

Q. How effective is certolizumab pegol in patients who have been recently diagnosed with Crohn's disease?

- A.** In PRECISE 2, we found that when certolizumab pegol is used earlier in the disease it tends to be more effective. Particularly high response rates were

observed for patients who had had Crohn's disease for less than 1 year; at Week 26, the response rate was 90% for certolizumab pegol and 37% for placebo. Nine out of 10 patients were in response at 6 months, and approximately 7 out of 10 were in remission. The results were still good among patients who had had Crohn's disease longer, but the rates drop off a little bit as the disease duration increases. Those patients having Crohn's disease for between 1 and 5 years had a response rate of 57% in the certolizumab pegol group compared with 37% in the placebo group. The corresponding remission rates were 44% and 24%, respectively. So again, this probably reflects the fact that patients are developing complications of Crohn's disease over time (such as strictures or penetrating disease) that are more refractory to treatment. It is evidence such as this that supports earlier intervention with biologic agents to prevent progression of the disease to more complicated disease states that are refractory to treatment.

Q. Now, moving on, what is the tolerability of certolizumab pegol?

A. Most patients tolerate certolizumab pegol very well. When you look at the data from clinical trials, there are few side effects of the medication. In PRECISE 2, the adverse effects that occurred slightly more with certolizumab pegol than with placebo included headaches, upper respiratory infections, and cough. Injection-site reactions or pain were both low (less than 3%) in the certolizumab pegol group.

Q. Do you consider certolizumab pegol to be a safe drug?

A. Certainly. Obviously, all medicines that suppress the immune system do have some risk associated with them (particularly the risk of infection). However, when you look at the PRECISE 2 trial, for instance, the rate of serious adverse events with certolizumab pegol was approximately the same as that for placebo. The rate of serious adverse events in placebo-treated patients was approximately 7%; the rate with certolizumab pegol was approximately 6%. Breaking these rates down into the type of serious adverse event shows that there was a slightly higher risk of serious infections in those patients treated with certolizumab

pegol (approximately 3%) compared with placebo (1%). Reassuringly, at least in the PRECISE 2 trial, there was no evidence of malignancy. Other effects that can be a cause for concern in patients who receive anti-TNF therapy, including the development of anti-double-stranded DNA or anti-nuclear antibodies and serum sickness-like reactions, occurred with very low frequency and at levels similar to placebo in PRECISE 2. It should be noted, however, that a single trial is not powered to detect uncommon and rare events such as opportunistic infection, malignancy, lupus-like reactions, and MS-like reactions.

Q. What is your personal experience with this new anti-TNF drug?

A. At our center, we have enrolled a number of patients into the PRECISE trials. Obviously, we do not know who has received placebo and who has received certolizumab pegol in the blinded phase of the trials. In addition, some of our patients have been receiving open-label certolizumab pegol for 2.5–3 years and most are continuing to do quite well. I am very pleased with how well certolizumab pegol works for our patients and look forward to seeing it become available outside of clinical trials (hopefully in the near future).

Q. Finally, how do you foresee the treatment of Crohn's disease in the coming years?

A. I think we are going to see an increasing use of biologic agents earlier in the course of the disease in order to prevent some of the complications I mentioned earlier: strictures, fistulizing disease, and the need for surgery. I think it will be a tremendous step forward and lead to improvement in quality of life. It will become less common for more aggressive treatment to commence only once complications occur. As we obtain more evidence on how to identify patients who are most at risk of developing some of these complications, we can intervene earlier and prevent these from occurring. So I am very optimistic. I think we are going to see tremendous improvements in treatment for these patients, particularly as we become more able to identify and stratify people based on their genetics or certain serologic evidence as to who is at risk of developing further problems.

Further reading

Certolizumab pegol overview

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PRECiSE 2

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PRECiSE I

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