# ADVANCES IN IBD

Current Developments in the Treatment of Inflammatory Bowel Diseases

Section Editor: Stephen B. Hanauer, MD

## The CHARM Trial of Adalimumab in Crohn's Disease

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### G&H Could you describe the design and designated endpoints for the CHARM trial?

**JC** The Crohn's Trial of the Fully Human Antibody Adalimumab for Remission Maintenance (CHARM) examined the anti–tumor necrosis factor (TNF) antibody adalimumab (Humira, Abbott Laboratories) for the maintenance of Crohn's disease remission. The objective of the study was to evaluate the efficacy and safety of adalimumab, in two different dosing regimens, in maintaining clinical remission in patients with moderate or severely active Crohn's disease who responded to adalimumab in open label induction. The design is similar to other trials of anti-TNFs for Crohn's: ACCENT for infliximab (Remicade, Centocor) and PRECISE-2 for certolizumab pegol (Cimzia, UCB Pharma). All three studies had an open-label phase, with randomization to either drug or placebo afterward.

CHARM was one of the largest studies of anti-TNF therapy, initially including 854 patients who received open label induction treatment with adalimumab, 80 mg at week 0 and 40 mg at week 2. Recent results from the CLASSIC I study by Hanauer and associates show that the more effective doses for induction therapy with adalimumab are 160 mg at week 0 and 80 mg at week 2. These are the doses that can be expected for use in clinical practice. However, at the start of CHARM, the CLASSIC I results were not yet available.

At week 4, 778 patients (both responders and nonresponders) remained and they were randomized to either adalimumab 40 mg weekly, adalimumab 40 mg every other week, or placebo, through week 56. Of this group, 499 were responders at week 4. These 499 patients were followed as the primary efficacy analysis group.

Primary endpoints for the trial were remission at week 26 and at week 56. Efficacy was measured in the same way as in the other trials mentioned above, with remission defined by a Crohn's Disease Activity Index (CDAI) score of less than 150. A number of secondary endpoints were also monitored, including maintenance of response, discontinuation of steroid use, fistula healing, and quality-of-life questionnaire score.

All patients were allowed background therapy during the trial. Concomitant treatments with 5-aminosalicylates, steroids, azathioprine, and methotrexate were permitted at stable dosing and previously exposed anti-TNF (infliximab) patients were also allowed but it was required that anti-TNF treatment be discontinued at least 12 weeks prior to study entry.

### G&H What were the primary efficacy findings of CHARM?

**JC** At week 26, 40% of the patients receiving adalimumab every other week and 46% of the patients receiving adalimumab weekly achieved clinical remission, whereas only 17% in the placebo group did. At week 56, the percentages maintaining remission were 36%, 41%, and 12%, respectively. When the remission curve is examined, it is clear that the rates of remission were well maintained through the course of the study. Beginning at week 8, the remission rate was superior in patients treated with adalimumab when compared to patients receiving placebo. In addition, there was no difference at any point between 40 mg weekly and 40 mg every other week. In my opinion, this study shows unequivocally that adalimumab can maintain remission in patients who respond to the drug and with a very nice plateau (ie, a small loss of effect over time). These results were not affected when analyzed in terms of previous anti-TNF exposure.

**G&H** Could you describe the most important secondary endpoint findings?

**JC** Among the secondary endpoints, two are significant. Of the patients receiving steroids at entry, approximately one third were weaned from steroid therapy in both the weekly and every other week adalimumab groups. In addition, approximately one third of patients receiving adalimumab achieved closure of fistulas as compared to only 13% of patients receiving placebo.

**G&H** What were the findings in CHARM in terms of safety?

**JC** When we consider safety, CHARM demonstrated very little of concern beyond what was already known about the safety of anti-TNFs. It is fair to say that when we look at overall adverse events, there were not more instances in either the placebo group or the adalimumab groups. In general, the adverse events were mild or moderate. There were two cases of tuberculosis in the adalimumab groups, and one of multiple sclerosis, which was already known to occur in patients receiving adalimumab. There was one death in the trial due to pulmonary embolism, which was probably not related to the drug. There were also some problems with injection-site reaction but these were generally mild. Withdrawal due to injection-site reaction occurred in only one patient.

**G&H** What is the mechanism of action for adalimumab?

**JC** All of the anti-TNFs have a similar mechanism of action in that they neutralize TNF. Infliximab and adalimumab are also known to induce apoptosis of TNF synthesizing cells such as lymphocytes and monocytes. It is believed this phenomenon of apoptosis is important in the mechanism of action in anti-TNFs. However, it has recently been shown that certolizumab, another anti-TNF, is also effective in treating Crohn's disease but certolizumab has not been shown to induce apoptosis. Therefore, it is not yet clear what is the most important mechanism of these drugs. There may be other mechanisms at play, which have yet to be discovered.

**G&H** Are there differences in efficacy among the different anti-TNF agents?

**JC** It is difficult to make scientific comparison among anti-TNFs because we still lack head-to-head comparison data. What we can do is look at the results of the placebo-controlled trials, keeping in mind that the designs were not exactly the same, the patient populations were not exactly the same, and background therapies differed. When we look at the three major maintenance trials, ACCENT, PRECISE-2, and CHARM, I think it is fair to say that the results are broadly similar in terms of efficacy.

When talking about previous anti-TNF exposure in CHARM, it is also important to note that none of the previously exposed patients had Crohn's disease that was primarily refractory to infliximab. Those patients initially responded to infliximab but had some loss of effect or intolerance. Therefore, we cannot say that adalimumab will work in patients who do not respond to infliximab.

**G&H** How do you see the results of CHARM affecting the use of anti-TNFs in clinical gastroenterological practice?

**JC** Anti-TNFs will most likely continue to be prescribed in patients who are either resistant to or intolerant of steroids and immunosuppressives. With the introduction of new drugs in this class and increasing ease in the mode of their administration, it is clear that there will be a tendency to expand these drugs' indications. However, we are not ready to start considering a "top-down" strategy, where we start the treatment of a new patient with Crohn's disease with anti-TNF therapy. Due to recent warnings about the side effects of these drugs, particularly the risk of lymphoma, we need to remember to be very cautious in prescribing them and to examine the risk:benefit ratio for each patient.

Overall, the results of CHARM mark an improvement of the drug class. The first agent was an intravenously administered chimeric antibody. Adalimumab is a humanized antibody, which is subcutaneously administered. It is an evolution of therapy but not a revolution. We are still left with those Crohn's disease patients who are refractory to all anti-TNF therapy.

**G&H** With the impending introduction of several new anti-TNFs, how will clinicians choose among them?

**JC** When it comes to the choice of anti-TNF, I think several parameters will be important. There are some safety issues that are class-related. Opportunistic infection and tuberculosis will be seen with all anti-TNF therapy. However, other side effects may be less frequently observed with adalimumab because it is a humanized antibody. Therefore, we may theoretically expect fewer immunogenicity problems. We may see injection site reactions but they will be for the most part milder and less frequent than the problems we observe with infusion reaction from infliximab. Also, it is not yet known if it will be necessary to use adalimumab with background immunosuppressive treatment. Infliximab is recommended for use with

azathioprine or methotrexate due to immunogenicity concerns. This may not be the case with adalimumab and if it can be prescribed alone it will have a great advantage in terms of safety.

Another consideration is the mode of administration. I suspect that the subcutaneous self-administration of adalimumab will give it an advantage over intravenous infusion of infliximab and possibly also over certolizumab, which currently requires nurse assistance. Cost will also be an issue but until adalimumab receives a gastroenterological indication and certolizumab reaches market, costs cannot be calculated.

## Suggested Reading


Van Assche G, Vermeire S, Rutgeerts P. Emerging biological treatments in inflammatory bowel diseases. *Dig Dis*. 2006;24:131-136.

Hanauer SB, Sandborn WJ, Rutgeerts P, et al. Human anti-tumor necrosis factor monoclonal antibody (adalimumab) in Crohn's disease: the CLASSIC-I trial. *Gastroenterology*. 2006;130:323-333; quiz 591.

Atzeni F, Turiel M, Capsoni F, et al. Autoimmunity and anti-TNF-alpha agents. *Ann N Y Acad Sci*. 2005;1051:559-569.


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