Biologic Therapy for Inflammatory Bowel Disease

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Disclosures

Introduction

In the year since Digestive Disease Week (DDW) 2006, we have seen the US Food and Drug Administration's (FDA) approval of infliximab for the treatment of ulcerative colitis[1] and adalimumab for the treatment of Crohn's disease.[2] Two additional biologic agents -- certolizumab pegol and natalizumab -- may be approved by the end of this year, and other agents are in the early stages of testing. The appropriate use of these medications with respect to concomitant immunomodulators, early intervention, and long-term maintenance was a major theme at this year's DDW meeting, as was the safety of these agents and their potential to reduce the rate of hospitalizations and surgeries. This report highlights the major studies presented at DDW 2007 regarding biologic therapy for inflammatory bowel disease, with a view toward their clinical implications.

New Biologics

Natalizumab

Natalizumab* is a recombinant, humanized immunoglobulin (Ig)G4 monoclonal antibody against alpha4 integrins. Prior studies, including ENACT (Evaluation of Natalizumab as Continuous Therapy)[3] and ENCORE (Efficacy of Natalizumab in Crohn's Disease Response and Remission)[4] have demonstrated the efficacy of this agent for the induction and maintenance of remission in patients with moderate to severely active Crohn's disease. However, safety concerns surrounding the estimated 1/1000 incidence of progressive multifocal leukoencephalopathy in patients exposed to natalizumab have delayed its approval in this setting.[5] During DDW 2007, further analysis of the ENCORE trial demonstrated that natalizumab was effective in the subpopulation of patients with prior infliximab exposure: among patients who had previously failed to respond to therapy with infliximab [n=172], 38% had a sustained response to natalizumab through weeks 8 and 12 compared with 15% of patients treated with placebo (P < .001).[6] In another study presented during this year's meeting, natalizumab was also found to be effective in patients with severe Crohn's disease.[7] Of those patients who entered the ENCORE trial with a baseline Crohn's Disease Activity Index (CDAI) score ≥ 330 (n=155), 51% had a sustained response to natalizumab through weeks 8 and 12 compared with 27% of patients treated with placebo (P = .002). Natalizumab was also found to be more effective than placebo for inducing and sustaining remission in Crohn's disease patients with early disease (ie, disease of ≤ 3 years' duration) in both the ENCORE and ENACT-2 trials.[8] Finally, in another analysis of the ENCORE trial, the rates of clinical response and remission at weeks 8 and 12 were statistically superior in the natalizumab-treated group compared with placebo, regardless of concomitant immunosuppressant use.[9]

CNTO 1275

CNTO 1275* is a fully human monoclonal antibody targeting the common p40 subunit of interleukin (IL)-12 and IL-23. In a 54-week, phase 2 study,[10] the safety and efficacy of either a single intravenous (IV) infusion or 4 subcutaneous injections of CNTO 1275 were evaluated in patients with moderate-to-severe Crohn's disease, including nonresponders to infliximab. Clinical response was defined as a reduction from baseline in the CDAI of ≥ 25% and ≥ 70 points. At week eight, 49.0% of patients receiving CNTO 1275 were in clinical response vs 39.6% who received placebo (P = .34; primary end point). At week 4 and at week 6, a total of 52.9% of patients receiving CNTO 1275 were in clinical response vs 30.2% receiving placebo (P = .02); 49.0% of patients receiving CNTO 1275 were in response at week 8 using ≥ 100-point CDAI reduction from
baseline vs 30.2% receiving placebo ($P = 0.05$). For patients who had previous infliximab exposure, 59.1% who received CNTO 1275 were in clinical response at week 8 compared with 25.9% who received placebo ($P = 0.02$). The study authors concluded that short-term treatment with this novel monoclonal antibody was generally well-tolerated and had a beneficial effect in patients with moderate-to-severe Crohn's disease. This effect was most prominent in patients with prior infliximab experience. One patient previously treated with infliximab developed histoplasmosis. There were no serious infections in the group without prior infliximab exposure.

**Visilizumab**

Visilizumab*, a humanized anti-CD3 monoclonal antibody, has shown some therapeutic efficacy in phase 1 trials of ulcerative colitis. [11] Hommes and colleagues[12] presented the results of an open-label, phase 1 study of visilizumab in patients with moderate-to-severe inflammatory nonfistulating Crohn's disease. Patients were administered an IV bolus of visilizumab 10 mcg/kg on 2 consecutive days. Clinical response was defined as a decrease in the CDAI of $> 100$ points below the subjects' baseline value, and remission was defined as a CDAI $< 150$ at day 59 from injection. The median baseline CDAI value was 397 (range, 271-516), and the median baseline C-reactive protein level was 28 mg/L (range, 2-70), suggesting a patient population with severe disease. Seventeen subjects had received prior infliximab therapy. Forty-four percent of patients had a clinical response to visilizumab at day 59, and 39% at 6 months. Remission by day 59 was achieved in 11% of subjects. Mild-to-moderate cytokine release syndrome occurred in the majority of patients.

**CCX282-B**

CCX282-B* is an orally active inhibitor of chemokine receptor CCR9, which is expressed by mucosa-homing intestinal leukocytes. CCR9 and its ligand CCL25 are implicated in the pathogenesis of Crohn's disease. This agent was investigated in a 71-patient, randomized, double-blind, placebo-controlled, phase 2 trial of patients with moderate-to-severe Crohn's disease; findings were presented during this year's DDW meeting. [13] Subjects were randomized to receive either CCX282-B 250-mg capsules or placebo in a 2:1 ratio. The agent was well tolerated, with an adverse event profile similar to placebo. Forty-nine percent of CCX282-B-treated patients had a 70-point decrease in CDAI compared with 45% on placebo. However, in the population of 39 patients with more active disease (baseline CDAI $\geq 250$ and C-reactive protein $> 7.5$ mg/L), a reduction of 70 points in CDAI occurred in 58% treated with CCX282-B vs 31% treated with placebo. A phase 3 trial is planned to confirm efficacy.

**Anti-Tumor Necrosis Factor (TNF)-alpha Therapy**

**Adalimumab**

Adalimumab, a fully human IgG1 anti-TNF-alpha monoclonal antibody that has been commercially available in the United States for rheumatoid arthritis, ankylosing spondylitis, and psoriatic arthritis, was FDA approved in early 2007 for reducing signs and symptoms and inducing and maintaining clinical remission in adult patients with moderately to severely active Crohn's disease who have had an inadequate response to conventional therapy and/or have lost response or become intolerant to infliximab. [14] Data presented during this year's DDW meeting demonstrated that adalimumab was highly effective in inducing remission in early Crohn's disease, suggesting that disease duration is a significant contributor to the likelihood of achieving remission. This subanalysis of the CHARM (Crohn's trial of the fully Human antibody Adalimumab for Remission Maintenance) trial stratified randomized responders by disease duration and assessed the effect of duration of disease on remission. [15] (CHARM was a double-blind, placebo-controlled, phase 3, multicenter, 56-week study evaluating the efficacy and safety of adalimumab in maintaining clinical remission in patients with moderate-to-severe Crohn's disease.) At week 26, remission rates for randomized responders with disease duration $< 2$ years were as follows: 17% for placebo vs 59% for adalimumab (data from the 2 adalimumab groups were pooled; $P < 0.05$ for adalimumab vs placebo). At week 56, the remission rates were 17% and 51%, for the placebo and adalimumab groups, respectively ($P < 0.05$ for adalimumab vs placebo).

In another analysis of the CHARM trial presented at DDW 2007, investigators evaluated the effect of adalimumab maintenance therapy on the risk of all-cause hospitalization in patients with moderate-to-severe Crohn's disease. [16] All patients who were randomized were included in this analysis. Using Kaplan-Meier curves, at 3 months, 13.4% of placebo patients had been hospitalized compared with 5.2% of adalimumab patients, for a relative rate reduction of 61%. At 12 months, 25.4% of placebo patients had been hospitalized compared with 12.9% of adalimumab patients, for a relative rate reduction of 49%. The only factor independently associated with a reduction in hospitalizations was treatment group (hazard ratio 0.309; $P < 0.01$).

A post-hoc analysis of the GAIN [17] (Gauging Adalimumab efficacy in Infliximab Nonresponders) trial, in which 325 Crohn's disease patients who had failed to respond to previous infliximab treatment were randomized to receive either placebo or adalimumab 160 mg at week 0 followed by 80 mg at week 2 subcutaneously, [18] assessed the time to symptomatic response to adalimumab.
Seven-day CDAI diaries were obtained at baseline and then at study weeks 1, 2, and 4. The 3 patient-reported diary components of the CDAI were summed and compared with placebo. Summation of these 3 patient-reported CDAI diary components was significantly different from placebo by day 4, and the significant difference was maintained throughout the remainder of the study for all available data points, demonstrating a rapid response to adalimumab in patients with prior infliximab exposure.

The safety of adalimumab across induction and maintenance datasets in Crohn's disease clinical trials was also reported during DDW 2007.[19] As of February 14, 2006, the adalimumab Crohn's disease clinical trial safety database contained data for 1459 patients representing 1506 patient-years of adalimumab exposure. The incidence and severity of adverse events, serious adverse events, and adverse events leading to discontinuation overall were similar in the induction and maintenance datasets. Two cases of demyelinating disease, 3 cases of tuberculosis, 1 case of congestive heart failure, 3 lupus-like cases, and 2 deaths (pulmonary embolus in an elderly patient with a history of arrhythmias and emboli; acute myeloid leukemia in a patient on azathioprine) were reported in adalimumab-treated patients. These data are similar to those reported for other agents in this class as well as to the extensive database for adalimumab in other indications.

Certolizumab Pegol

Certolizumab pegol* is a humanized anti-TNF Fab' monoclonal antibody fragment linked to polyethylene glycol. The PRECiSE (Pegylated antibody fRagment Evaluation in Crohn's disease Safety and Efficacy) 1 and 2 trials demonstrated the efficacy of this agent in the induction of response and maintenance of response in patients with moderately to severely active Crohn's disease.[20,21]

Further analysis of PRECiSE 2, the phase 3 trial that evaluated the efficacy and tolerability of certolizumab pegol in the maintenance of clinical response following successful induction therapy in patients with active Crohn's disease (CDAI > 220), was presented during DDW 2007.[22] In the 6-week induction period, patients received open-label certolizumab pegol 400 mg at weeks 0, 2, and 4. In this current subgroup analysis of PRECiSE 2, clinical response (defined as CDAI of ≥100 points) rates at week 6 were similar in patients with or without concomitant corticosteroid use (62.9% vs 64.8%, respectively) or immunosuppressant use (66.3% vs 62.7%). Remission rates also did not differ substantially between subgroups. Thus, these findings demonstrate a rapid response to certolizumab pegol and suggest that concomitant baseline medications did not have an impact on response and remission rates at week 6.

Efficacy results from PRECiSE 3, an open-label extension study that recruited patients from PRECiSE 1 and PRECiSE 2, were also presented at DDW 2007.[23] Subjects received certolizumab pegol...