TNF Blocker May Help Crohn's Disease

BY DAMIAN McNAMARA
Miami Bureau

ORLANDO — Endoscopic improvement occurred in more than 60% of Crohn's disease patients after 10 weeks of treatment with a pegylated biologic agent, certolizumab pegol. The study was the first prospective, phase III, multicenter, open-label study of the drug in such patients.

The tumor necrosis factor (TNF) blocker also led to improved clinical scores and histologic response among patients with moderate to severe disease.

The investigators showed that Cimzia (certolizumab pegol) was associated with endoscopic improvement in 62% of patients at week 10.

They also assessed endoscopic remission, defined as a Crohn's Disease Endoscopic Index of Severity (CDEIS) score decrease of at least 7 points from baseline.

"We confirmed clinical efficacy, with 42% of patients in remission at week 10," said Dr. Jean-Frederic Colombel, a hepatogastroenterologist at Centre Hospitalier Universitaire de Lille (France). He is a consultant and on the advisory board for UCB Pharma, which initiated and analyzed the study.

Cimzia was approved by the U.S. Food and Drug Administration in April 2008 for the reduction of signs and symptoms of Crohn's disease and the maintenance of clinical response in adult patients with moderately to severely active disease who have had an inadequate response to conventional therapy.

In the study, 51% of the initial 89 participants were on immunosuppressant therapy and 42% were taking corticosteroids. Participants started with a CDEIS score of 8 or greater, ulcerations in at least two segments, and a Crohn's Disease Activity Index (CDAI) score between 220 and 450. "This is one of the most severe populations studied," Dr. Colombel said at the annual meeting of the American College of Gastroenterology.

The primary outcome, change in CDEIS scores, showed improvement from a mean of 15 at baseline to 8 at week 10. This was "highly significant," Dr. Colombel said. He presented these first, 10-week results of the ongoing endoscopic Mucosal Improvement in Patients with Active Crohn's Disease (MUSIC) study, and said the 54-week results are pending.

Mean duration of Crohn's disease in study participants was 8 years, mean age was 30 years, and 30% were men. A total of 71 patients (80%) experienced an adverse event during the study in an intent-to-treat analysis, including 37 patients with a drug-related event. Nine participants discontinued treatment before 10 weeks—two citing lack of efficacy, and seven because of adverse events.

Participants received subcutaneous injections of certolizumab pegol 400 mg at weeks 0, 2, and 4 and then every 4 weeks. After week 10, depending on CDEIS response, some patients switched to injections every 2 weeks, Dr. Colombel said.

A meeting attendee asked about the rationale for increasing administration to every 2 weeks. "The induction regimen is the same used in clinical practice," Dr. Colombel said. "For this short-term data, we did not escalate the dose. For the long-term data, there is evidence that you can go from every 4 to every 2 weeks. That is what we are doing with the 54-week data."

At baseline, 92% of the patients had deep intestinal ulcerations; this percentage decreased to 42% at week 10. In addition, 5% had superficial lesions detected at study entry, and this increased to 31% at week 10, Dr. Colombel said.

Compared with baseline, histologic Crohn's disease scores decreased a mean of 2.7 points in the colon and 2.8 points in the ileum at 10 weeks. In addition, 46% of patients achieved clinical remission, defined as a decrease in CDAI baseline scores of 150 points or more by 10 weeks.

A meeting attendee asked if the single-arm study design is a limitation. "Good question," Dr. Colombel said. "It's quite difficult to put patients in a placebo-controlled study because anti-TNF is available, and they need three endoscopies in 1 year.

"What we also plan to do is look at videotapes in a blinded way, and do the same thing with histology—which will significantly improve the value of the data," he added. ■

THE EFFECTIVE PHYSICIAN

Reducing Gastrointestinal Risks of NSAID Therapy

BY WILLIAM E. GOLDEN, M.D., AND ROBERT H. HOPKINS, M.D.

Background

Antiplatelet agents are being used more frequently and for more prolonged durations; as a result, it is vital for clinicians to know the associated risk of gastrointestinal bleeding and strategies to minimize this risk. A consensus panel was recently convened by the American College of Cardiology Foundation, the American Heart Association, and the American College of Gastroenterology to provide guidelines.

Conclusions

Nonsteroidal anti-inflammatory drugs (NSAIDs), including aspirin, are among the most widely used medications in the United States; surveys of adults aged 65 years and older show that 70% take these agents at least weekly and that more than a third use them daily, for both cardiac and noncardiac indications.

Aspirin, like all NSAIDs, causes direct gastrointestinal (GI) mucosal injury as well as systemic effects resulting from prostaglandin depletion.

Low-dose aspirin for cardiac prophylaxis is associated with a two- to fourfold increase in the risk of adverse GI events, which increases in proportion to the aspirin dose. Enteric-coated or buffered aspirin preparations do not reduce the risk of gastrointestinal bleeding.

The addition of a cyclo-oxygenase-2–specific NSAID to preventive doses of aspirin (325 mg or less) imparts the same ulcer risk as use of a nonselective NSAID.

There is little human data on the potential for GI mucosal injury with clopidogrel monotherapy. Although clopidogrel may not directly cause upper-GI ulcers, its antiangiogenic effects may impair the healing of mucosal damage caused by other medications or *Helicobacter pylori* infection. This may ultimately result in clinically significant ulcers and ulcer complications. The use of clopidogrel with a NSAID (including low-dose aspirin) has been associated with an increase in serious upper GI adverse events.

Prostaglandin depletion is the primary mechanism for NSAID-induced gastrointestinal injury. Misoprostol, a synthetic prostaglandin, is the sole drug approved by the Food and Drug Administration for the prevention and treatment of NSAID-induced ulcers and complications; however, it is rarely used because of the high prevalence of side effects.

Sucralfate has been shown to be effective for the treatment of NSAID-induced duodenal ulcers, but it is ineffective for treatment or prevention of NSAID-associated gastric ulcers. Histamine$_2$ antagonists at standard dosage do not reduce gastric pH sufficiently to prevent NSAID-related gastric ulcers.

Implementation

Patients who are aged 60 years and older, those who require systemic corticosteroid therapy, and those who have dyspepsia and/or gastroesophageal reflux symptoms are at increased risk of GI bleeding with antiplatelet treatment.

Proton pump inhibitors (PPIs) are the preferred drugs for treatment and prevention of aspirin- and other NSAID-induced gastrointestinal injury.

A gastroprotective agent should be coprescribed in patients at risk of gastrointestinal complications who are treated with cardiac-dose aspirin plus any NSAIDs, including over-the-counter doses, or celecoxib.

For chronic cardiac chemoprophylaxis, dosages of aspirin larger than 81 mg daily should not be used routinely; this strategy provides a balance of cardiac benefit and minimizes the gastrointestinal risk.

Patients treated with aspirin and anticoagulants (including warfarin, heparin, and low-molecular-weight heparins) have a significantly increased risk of bleeding. Concomitant PPI treatment is recommended to reduce the risk of upper GI bleeding.

Clopidogrel should not be substituted for aspirin in patients who have previous ulcer bleeding in an effort to reduce the risk of recurrent ulcer bleeding. The combination of aspirin and a PPI has a lower risk of upper GI bleeding than does clopidogrel monotherapy.

In patients with high bleeding risk who require a coronary stent, a bare-metal stent—with its shorter requirement for dual antiplatelet therapy—may be preferable.

The combination of clopidogrel and warfarin is associated with more major bleeding than is monotherapy with either of these drugs alone. Clopidogrel plus warfarin and the combination of warfarin, clopidogrel, and aspirin should be considered only in patients in whom the benefit is likely to outweigh the significant bleeding risks. The international normalized ratio should be maintained at the lowest level appropriate for the clinical situation, usually 2.0-2.5; coprescribing a PPI may help mitigate the GI bleeding risk.

Patients with a history of ulcer and/or ulcer bleeding who require chronic antiplatelet treatment should be tested for *H. pylori* infection and treated to eradicate the infection, if it is found. This recommendation has been controversial, but current evidence suggests this strategy reduces the risk of recurrent ulcer bleeding.

The decision to discontinue aspirin in patients with acute ulcer bleeding must be individualized based on assessment of the patient's risk of cardiac complications balanced with the risk of continued bleeding. To date, this dilemma has been addressed by only one trial that suggested a significant increase in all-cause mortality with aspirin discontinuation and a trend toward more rebleeding in those in whom aspirin was continued.

Reference

Bhatt DL, et al. ACCF/ACG/AHA 2008 expert consensus document on reducing the gastrointestinal risks of antiplatelet therapy and NSAID use: A report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents. Circulation 2008;118:1894-909.

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