

Recent Trends of Infliximab Treatment for Crohn's Disease

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Crohn's disease is a chronic inflammatory disorder of the gastrointestinal tract and characterized by relapsing and remitting episodes, with progression over time to complications of stricture, fistulas, or abscesses. The etiology is unknown, although the common opinion is that the disease arises from a disordered immune response to the gut contents in genetically predisposed individuals. Infliximab is a mouse-human chimeric antibody against tumor necrosis factor α , and has proven to be effective in active Crohn's disease for both induction and maintenance therapy. Despite the growing experience with infliximab in Crohn's disease, optimal treatment strategies still need to be determined. The purpose of this review is to summarize the current knowledge on the use of infliximab in Crohn's disease and to discuss the yet-unsolved issues. (**Pediatr Gastroenterol Hepatol Nutr 2012; 15: 19~22**)

Key Words: Crohn's disease, Infliximab

INTRODUCTION

Crohn's disease (CD) is a chronic inflammatory disorder of the gastrointestinal tract and characterized by relapsing and remitting episodes, with progression over time to complications of stricture, fistulas, or abscesses [1-3]. The ultimate treatment goal in the management of CD should be to strive to change the underlying course of CD and restore normal bowel function [4-6]. Infliximab is a mouse-human chimeric antibody against tumor necrosis factor α , and has proven to be effective in active CD for both induction and maintenance therapy [7-9]. Since receiving FDA approval for

pediatric use in May 2006, infliximab has been widely used in pediatric patients with CD [10-12].

CLINICAL DATA OF INFLIXIMAB IN LUMINAL CD

The ACCENT (A Crohn's disease Clinical trial Evaluating infliximab in a New Long-term Treatment regimen) I trial demonstrated the efficacy of infliximab in luminal CD [7]. This largest and most comprehensive study of maintenance therapy was a multicenter, randomized, double-blind, international trial studying retreatment and maintenance of remission in patients with CD treated with

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infliximab. In this study, 573 patients with active CD (Crohn's Disease Activity Index (CDAI) 220–400) received a single infusion of infliximab 5 mg/kg. At week 2, patients responding to infliximab were randomized to receive either episodic (infliximab 5 mg/kg infusion followed by placebo infusions at weeks 0, 2 and 6 and then every 8 weeks) or scheduled treatment (infliximab 5 mg or 10 mg/kg at weeks 0, 2 and 6 and then every 8 weeks). ACCENT I showed that scheduled infliximab treatment every 8 weeks is more effective than episodic treatment and formed the basis for infliximab dosing. In addition, scheduled infliximab was associated with fewer hospitalizations and higher rates of mucosal healing.

CLINICAL DATA OF INFLIXIMAB IN FISTULIZING CD

The ACCENT II trial demonstrated that infliximab is effective in treating fistulizing CD [13]. In this double-blind, placebo-controlled trial, 306 adult patients with CD and one or more draining abdominal or perianal fistulas of at least 3 months' duration were randomized. Systematic treatment with infliximab 5 mg/kg every 8 weeks was superior to placebo in both improvement and closure of draining fistulas over 54 weeks. ACCENT II also demonstrated that infliximab significantly reduces the rate of hospitalization and surgery in patients with fistulizing CD.

The ACCENT I and ACCENT II studies have shown that scheduled maintenance therapy with infliximab is superior to episodic therapy to maintain response and remission, both in luminal and in fistulizing CD.

USE OF IMMUNOSUPPRESSIVE AGENTS IN COMBINATION WITH INFLIXIMAB

There are conflicting opinions regarding the use of immunosuppressive agents in combination with infliximab due to several safety reports. The GETAID (Grouped'Etude Therapeutique des Affections In-

flammatoires Digestives) study demonstrated the benefits of initiating infliximab treatment earlier by showing that infliximab plus azathioprine combination therapy is more effective than azathioprine monotherapy in azathioprine-naive patients [14]. Data from the SONIC (The Study of Biologic and Immunomodulator Naive Patients in Crohn's Disease) study demonstrated that patients with moderate to severe CD treated with azathioprine 2.5 mg/kg/day in combination with infliximab 5 mg/kg at weeks 0, 2, and 6 and then every 8 weeks, or infliximab alone, are more likely to have a glucocorticoid-free clinical remission than those on azathioprine alone (57% and 44% vs 31%, respectively) [15]. Interestingly, in this study, infliximab combination therapy was more effective in inducing steroid-free clinical remission than infliximab monotherapy ($p=0.022$). These effects were sustained through to week 50. SONIC demonstrated that an infliximab-based treatment strategy is more effective than azathioprine monotherapy in azathioprine-naive patients.

CLINICAL EFFICACY OF INFLIXIMAB IN PEDIATRIC CD

The largest randomized study in children was the REACH (A randomized, multicenter, open-label study to evaluate the safety and efficacy of anti-TNF chimeric monoclonal antibody in pediatric subjects with moderate-to-severe Crohn's disease) study. It was an industry-driven prospective, open-label investigation of a three-dose induction with infliximab in moderate to severely active pediatric CD, followed by doses at either 8- or 12-week intervals for maintenance [16]. At baseline, 112 patients on concomitant immunosuppression received an induction regimen of 5 mg/kg infliximab at weeks 0, 2, and 6. At week 10, 103 patients were randomized to receive infliximab maintenance treatment every 8 weeks ($n=52$) or every 12 weeks ($n=51$). The REACH study demonstrated that maintenance therapy every 8 weeks was superior to every 12 weeks in maintaining clinical response and remission in pediatric CD.

SAFETY OF INFLIXIMAB IN CD

The downside of immunosuppressive agents in combination with infliximab may be an increased risk of toxicity. With the reports on hepatosplenic T-cell lymphoma (HSTCL) in predominantly young male patients on combination therapy [17,18], many pediatric gastroenterologists converted to infliximab monotherapy after a short duration of combination therapy. However, according to the SONIC trial [15], the incidence of adverse events (including serious adverse events) and serious infections was similar among the infliximab monotherapy, infliximab plus azathioprine combination therapy and azathioprine monotherapy groups. However, infusion reactions occurred less frequently among patients receiving combination therapy than among those receiving infliximab monotherapy. Therefore, the choice of infliximab monotherapy or combination therapy in patients who have not received such therapy previously is an individualized benefit-risk decision. Prospective, observational studies with longer follow-up, such as the TREAT (The Crohn's Therapy, Resource, Evaluation, and Assessment Tool) registry [19], will continue to provide more useful information on this issue, and clinicians need to remain aware of the potential for serious adverse events during longer-term exposure beyond the confines of clinical trials.

THE EXPERIENCE IN SAMSUNG MEDICAL CENTER

We have used infliximab as an induction therapy since 2005. Our patients had a better response to infliximab treatment than compared to conventional therapy. At 8 weeks, remission was achieved in 3 of 11 patients (27.3%) in the step-up group, and in 16 of 18 patients (88.9%) in the top-down group. At 1 year of follow-up, remission was maintained in 5 of 11 patients (45.5%) and in 15 of 18 patients (83.3%) in the step-up and top-down groups, respectively [20]. At the 1 year

follow-up, the relapse rate (23.1%, 3 of 13 patients) in the top-down group was lower than that (61.5%, 8 of 13 patients) in the step-up group ($p=0.047$). At 2 years follow-up, the relapse rate (38.5%, 5 of 13 patients) in the top-down group was lower than that (76.9%, 10 of 13 patients) in the step-up group ($p=0.047$) [21].

CONCLUSION

Over the past 10 years, infliximab has been of great benefit to many adult and pediatric CD patients. This biological drug has proven to be efficacious in inducing and maintaining remission, achieving mucosal healing, inducing perianal fistula closure, reducing corticosteroid exposure, promoting growth, and improving quality of life. Concomitant use of immunomodulators may improve the clinical outcomes, but this potential benefit needs to be weighed against a possibly increased risk of malignancies, especially HSTCL. Therefore, a randomized controlled trial examining the efficacy and safety of infliximab as monotherapy versus combination therapy, such as the SONIC trial, in pediatric CD patients is needed.

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