

Infliximab therapy in pediatric Crohn's disease: a review

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Abstract: Anti-tumor necrosis factor alpha (TNF- α) therapy has re-defined our treatment paradigms in managing patients with Crohn's disease (CD) and ulcerative colitis. Although the ACCENT studies showed proven efficacy in the induction and maintenance of disease remission in adult patients with moderate to severe CD, the pediatric experience was instrumental in bringing forth the notion of "top-down" therapy to improve overall clinical response while reducing the risk of complications resulting from long-standing active disease. Infliximab has proven efficacy in the induction and maintenance of disease remission in children and adolescents with CD. In an open-labeled study of 112 pediatric patients with moderate to severe CD, 58% achieved clinical remission on induction of infliximab (5 mg/kg) therapy. Among those patients who achieved disease remission, 56% maintained disease remission on maintenance (5 mg/kg every 8 weeks) therapy. Longitudinal follow-up studies have also shown that responsiveness to infliximab therapy also correlates well with reduced rates of hospitalization, and surgery for complication of long-standing active disease, including stricture and fistulae formation. Moreover, these children have also been shown to improve overall growth while maintaining an effective disease remission. The pediatric experience has been instructive in suggesting that the early introduction of anti-TNF- α therapy may perhaps alter the natural history of CD in children, an observation that has stimulated a great deal of interest among gastroenterologists who care for adult patients with CD.

Keywords: Crohn's disease, infliximab, pediatric

Introduction

Crohn's disease (CD) and ulcerative colitis are chronic inflammatory intestinal disorders affecting 1.7 million people in North America.¹ Recent studies have shown an increasing incidence of CD in children, and an overall prevalence of 10% to 25% of all patients with inflammatory bowel disease (IBD).^{2,3} CD is characterized by patchy transmural inflammation involving any segment of the gastrointestinal tract from the mouth to the anus. Patients will typically show recurrent clinical exacerbations marked by symptoms of abdominal pain, diarrhea, and rectal bleeding, alternating with episodes of quiescent disease. Children often manifest constitutional signs of weight loss, growth failure and pubertal delay that may in part be secondary to extensive proximal small bowel disease of increased severity. Moreover, pediatric CD is often associated with extra intestinal manifestations, including arthritis, episcleritis, uveitis and erythema nodosum.¹

Although the principal goal of therapy is to induce and maintain an effective disease remission, the intestinal mucosa will often show ongoing inflammation that contributes

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to frequent relapses and less than favorable maintenance of clinical remission. Since CD may progress from intestinal inflammation to strictures and penetrating disease, including fistulas and abscess formation, mucosal healing has become a primary treatment objective. Since delayed puberty and growth failure is seen in 15% to 40% of pediatric patients with CD,⁴ achieving normal growth and development also represents an important end-point to therapy. The ultimate goal is to achieve and sustain an effective disease remission that avoids complications associated with long-standing and unremitting disease. To achieve this clinical objective is of paramount importance in order to improve patient quality of life, and avoid psychological complications, including anxiety, and depression. Given the myriad of potential therapies available to treat patients with CD, it has become increasingly important to select those medications with the most favorable benefit risk ratio that will minimize the overall need for corticosteroids (Figure 1).

Non-biological therapy

Enteral nutrition has proven efficacy in inducing disease remission in children with active CD,⁵ as well as preventing disease relapse in 60% to 75% of patients within a year.^{6,7} Although enteral nutrition is effective in inducing disease remission and in reversing micronutrient deficiencies, these treatment formulas are unpalatable and often require nasogastric or gastrostomy tube placement. Typically, adolescent patients are non-adherent to the prolonged implementation of nutritional therapy. They often object to the placement of these feeding tubes or the exclusivity of enteral nutritional therapy during periods of quiescent disease.⁵⁻⁷

Thomsen and coworkers showed in a double blind multicenter study of 182 adults with CD that mesalamine was

able to induce remission in 45%, 42% and 36% of patients with mild to moderate disease at the end of 8 weeks, 12 weeks and 16 weeks, respectively.⁸ However, de Franchis and coworkers showed that once patients achieved disease remission on mesalamine, less than 50% of patients were able to sustain disease remission after one year of maintenance therapy.⁹

Although studies have shown that corticosteroids are effective in inducing remission in patients with active CD,¹⁰ not all patients respond favorably. And among those patients that respond to induction corticosteroids, 40% to 68% of patients will relapse within a year, while up to 36% of patients will develop corticosteroid dependency.¹¹⁻¹⁴ This observation is also underscored by the detrimental impact of long-term corticosteroid use on patient growth and development.

Immunosuppressant drugs, including methotrexate, azathioprine (AZA), and 6-mercaptopurine (6-MP) are all effective in maintain disease remission in 40% to 65% of patients with corticosteroid-dependent moderate to severe CD.¹⁵⁻¹⁸

Biological therapy

In comparison, the biological agents used in CD include: the anti-tumor necrosis factor alpha (TNF- α) agents infliximab, adalimumab and certolizumab pegol (Figure 2) and anti-adhesion molecule drugs. All of these biological agents have been shown to be effective in children with CD. Herein, our focus will be on the role of infliximab in treating pediatric CD.

TNF- α

Over the last several years, our understanding of the pathogenesis of CD has improved remarkably with the development of several animal models. Indeed, the pro-inflammatory cytokine TNF- α is known to play an important role in CD,¹⁹ and has led to the development of several novel treatment strategies, including infliximab. TNF- α can transmit signals between immune cells leading to inflammation, thrombosis and fibrinolysis. Various stimuli, including bacterial endotoxin, radiation and viral antigens can bring on the release of secretory TNF- α from monocytes, macrophages and T-cell lymphocytes. As a potent pro-inflammatory cytokine, TNF- α must be firmly regulated; and failure to do so, allows for an unmediated inflammatory response.²⁰ In patients with CD, TNF- α is highly localized to the intestinal mucosa and lumen. Indeed, high concentrations have been measured in the lamina propria of the bowel of patients with CD²¹ and increased concentration of TNF has also been found in the stool of children with CD.²² At the

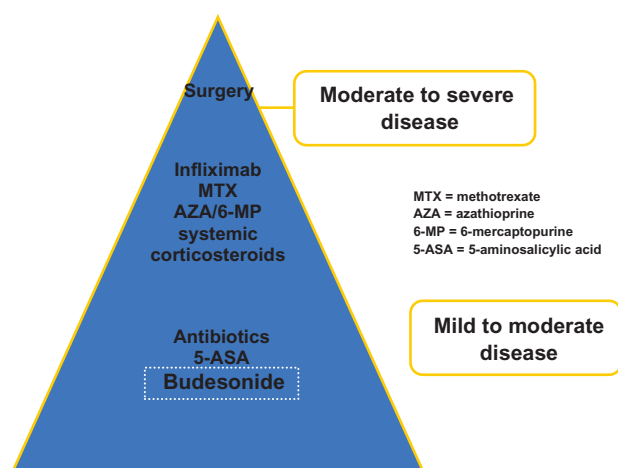


Figure 1 Crohn's disease practice guideline: pharmacologic pyramid.

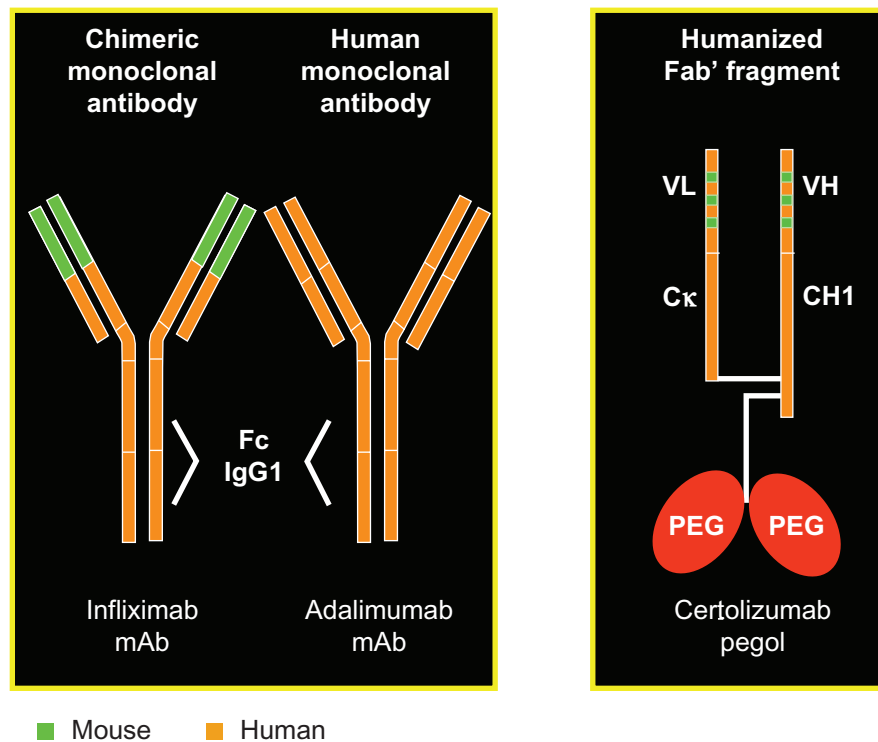


Figure 2 Anti-TNF- α structure of 3 biological therapies to treat Crohn's disease.

level of the mucosa, TNF- α recruits circulating inflammatory cells to the intestinal tissue, inducing tissue edema, coagulation activation through thrombin activation and granuloma formation. The migration of neutrophils is further facilitated through the increased expression of adhesion molecules and IL-8 by endothelial cells. TNF- α is pivotal in the formation of granulomas, one of the histological hallmarks of CD. Through its up-regulation of monocyte chemo-attractant protein-1, monocytes are recruited into the site of granulomatous inflammation. CD4 T-cell lymphocytes are the probable source for TNF- α production, as well as other cytokines involved in the so-called TH1 response, including interferon- α at the site of granulomas.

Infliximab

Infliximab is a chimeric IgG-1 monoclonal antibody with a high specificity for TNF- α . It induces apoptosis of TNF-producing cells, and promotes antibody dependent and complement dependent cytotoxicity.²³⁻²⁵ It has been shown to decrease histologic and endoscopic disease activity and in inducing and maintaining remission in patients with active CD. ACCENT I was a multicenter randomized double-blind international trial studying retreatment and remission maintenance in adult patients with CD treated with infliximab. Patients in this study were divided into 3 groups: patients given a single 5 mg/kg infusion,

patients given 5 mg/kg every 8 weeks, and patients given 10 mg/kg every 8 weeks for maintenance of remission. After 54 weeks, the initial clinical response was maintained in only 17% of patients in the single dose group compared to 43% of patients maintained on 5 mg/kg every 8 weeks and 53% of patients maintained on 10 mg/kg every 8 weeks. In addition, successful steroid-tapering was seen in only 9% of patients in the single dose group compared to 28% in the 5 mg/kg every 8 weeks group, and 32% of patients in the 10 mg/kg every 8 weeks group.²⁶

It has been the practice in many institutions, including our own to initiate maintenance anti-TNF- α therapy in patients that have shown clear refractoriness to either long-term 6-MP or AZA therapy. All of the studies, including ACCENT, CHARM and PRECISE have not shown any potential role of combining anti-TNF- α with anti-metabolite therapy. Moreover, the increasing concern of hepatic T-cell lymphoma has led many physicians to consider discontinuing either 6-MP or AZA with the introduction of biological therapy.²⁷ Although all anti-TNF α therapies have antigenic properties, those patients on infliximab therapy are most vulnerable. The concurrent use of immunosuppressive therapy has in the past been shown by Rutgeerts and coworkers to maintain a favorable clinical response to maintenance infliximab therapy, presumably due to the prevention of human anti-chimeric antibody (HACA) antibody formation.

In that study, 75% (12/16) of patients on concurrent 6-MP maintained a favorable clinical response, compared to 50% (9/18) on no concurrent immunosuppressive therapy.²⁸ In the ACCENT 1 study, only 18% of the patients on neither concurrent prednisone nor immunosuppressive drug therapy developed HACA, compared to just 10% of patients on concurrent azathioprine or methotrexate therapy.²⁶ The therapeutic benefit of concurrent immunosuppressive therapy is generally considered marginal and is felt to not outweigh the associated increased risk of hepatic T-cell lymphomas, a malignancy that is universally lethal in the pediatric patient population.²⁷ Moreover, both adalimumab and certolizumab have proven efficacy in salvaging those patients who develop either a partial responsiveness or intolerance to infliximab therapy.²⁸ As a result, the purported benefit is not felt to outweigh the increased risk for malignancy.

Other drug safety issues with infliximab include the development of anti-neutrophil antibodies and anti-double stranded DNA in 34% and 56% of patients on maintenance infliximab therapy, respectively. Furthermore, the long-term risk in developing systemic lupus is unknown, and may have an increased bearing on the African-American population. Other noteworthy long-term safety issues include the risk of super-infection (32%) and the risk of tuberculosis.¹¹

Adalimumab

The immunogenicity of infliximab has led to the development of other less immunogenic TNF inhibitory agents, including adalimumab and certolizumab. Adalimumab (fully human anti-TNF) has recently received approval for the treatment of active CD. Several studies have shown adalimumab to be superior to placebo for inducing and maintaining remission. It has also been shown to spare corticosteroids and salvage those patients with CD recalcitrant to infliximab therapy with an excellent safety profile. Unlike infliximab, adalimumab is prescribed as a subcutaneous injection every 2 weeks as a maintenance therapy.^{28,29}

Infliximab use in children

Studies evaluating the safety and efficacy of infliximab in children were first reported in several non-randomized studies.³⁰⁻³⁴ These initial studies showed that the response and remission rates (both partial and complete) were far superior compared to conventional therapy. Interestingly, its efficacy in children appeared to be higher than in adult.^{31,32}

In a multicenter, open-label, dose-blinded trial (n = 21), Baldassano and coworkers demonstrated the efficacy and safety of a single infusion of infliximab in the treatment of

pediatric CD. During the 12-week duration of the study, 100% achieved a clinical response and 48% achieved clinical remission, with significant improvements in the pediatric CD activity index (PCDAI), modified CDAI, erythrocyte sedimentation rate, and other outcome variables of interest. There were no infusion reactions in any of the patients and it was suggested that infliximab may be safe and effective as short-term therapy of medically refractory moderate to severe CD.³⁵ A prospective study published by Cezard and coworkers also explored the efficacy and toxicity of infliximab in children with severe CD. Twenty-one children (median age 15, range 13 to 17) were treated with infliximab with an induction sequence of 5 mg/kg at 0, 15, and 45 days. Nineteen children were in complete remission (defined as Harvey-Bradshaw index (HBI) <4) on day 45. 14/21 patients had stopped taking steroids at 3 months, and all had stopped parenteral nutrition. All perianal fistulas (n = 12) were also closed by day 90 and the drug appeared to be well tolerated.³⁶

Much evidence at present comes from retrospective analysis of children treated with infliximab, often as a rescue medication. In a retrospective study in children and adolescents with either corticosteroid dependent or resistant CD, patients were randomized to receive 1 to 3 infusions of infliximab (5 mg/kg/dose) over a 12-week period. The mean daily prednisone dosages decreased significantly in all the patients ($P < 0.01$) studied. A significant initial improvement (as assessed by a significant decline in PCDAI value) was noted in all subjects ($P < 0.0001$). Interestingly, over the subsequent 8-week period, 8 of 19 treated subjects had worsening of symptoms.³⁷ Lamireau and coworkers described yet another retrospective study in 88 children and adolescents (median age: 14, range: 3.3 to 17.9) treated with infliximab for active disease (66%) and/or fistulas (42%) that were refractory to corticosteroids (70%), and/or other immunosuppressive (82%) agents, and/or parenteral nutrition (20%). Patients received a median of 4 (1 to 17) infusions of 5 mg/kg of infliximab during a median time period of 4 months (1 to 17 months). From day 0 to day 90, the Harvey-Bradshaw score decreased from 7.5 to 2.8 ($P < 0.001$), with a significant decrease in both C-reactive protein and ESR ($P < 0.001$). At day 90 after the first infusion of infliximab, 49% of patients had symptom improvement, 29% were in remission; 53% of patients could be weaned off of corticosteroids and 92% off of parenteral nutrition.³⁸ The authors in both these studies concluded that treatment with infliximab was well tolerated and effective in most children and adolescents with CD refractory to conventional immunosuppressive therapy. No serious events were noted in any of these studies.

The Food and Drug Administration (FDA) approval for the use of infliximab therapy in pediatric CD was based on the results of the much publicized REACH clinical study, a randomized, multicenter, open-label study to evaluate the safety and efficacy of anti-TNF- α antibody in pediatric subjects with moderate to severe CD. A total of 112 pediatric patients (ages 6 to 17 years) with moderate to severe CD who took part in this study received infliximab at 5 mg/kg at week 0, 2 and 6. Patients who showed symptom improvement, or response, were then randomized to 2 groups and received infliximab every 8 or 12 weeks for almost 1 year. A concurrent immunomodulator was also required. At week 10, 88% patients showed response (defined as decrease from baseline in the PDAI score ≥ 15 points; total score ≤ 30) and 58% patients achieved clinical remission (defined as PDAI score ≤ 10 points). At week 54, 63% and 56% patients receiving infliximab every 8 weeks were in clinical response and clinical remission, respectively, compared with 33% and 23% patients receiving treatment every 12 weeks ($P = 0.002$ and $P < 0.001$, respectively). The data from this important prospective trial thus suggested that infliximab is not only highly effective in inducing clinical response and remission but also in maintenance of remission, more so with an 8-week dosing compared with every 12-week dosing.³⁹ The same research consortium also found infliximab to be an effective therapy in children with perianal disease, including patients with perianal fistula,⁴⁰ and in prolonging the withdrawal of corticosteroids over a 3-year follow-up period.⁴¹ Similar observations have also been made in an European study in children with CD. In that study, children on an on-demand treatment schedule were more-likely to experience a relapse (92%) when compared to patients on 2-month infusion schedule (23%).⁴²

Immunogenicity

HACA is the common side effect of infliximab infusion. The antibody is as a result of murine component of chimeric infliximab. However, adalimumab a fully human anti-TNF- α drug also has similar side-effects. In the REACH study, 2.9% (3 patients) developed HACA when compared to 35% on other trials.^{39,43-45} This could be explained by patients in the REACH study receiving concurrent immunosuppressive medication. Seventy-seven percent of patients in the REACH had inconclusive HACA results. HACA causes infusion reactions (acute and delayed), shortened response and also loss of response. Risk factors for development of HACA are single and episodic infusion, female gender, long gap between first and second infusion, and previous infusion

reaction. Studies suggest that it can be minimized by giving maintained therapy, a concomitant immunosuppressive agent, and corticosteroid.^{44,45}

Acute infusion reaction occurs in 11% to 8% patients and at 2.5% to 5.3% per infusion depending on the dosing method and concomitant treatment.^{39,46-48} Patients develop pruritus, chest pain, nausea, headache, and flushing within 24 hours. Antihistamines and/or corticosteroids do not prevent the infusion reaction. However, infusion reaction can be controlled by slow infusion, along with administration of antihistamine and corticosteroids. It is our general practice to pre-medicate those patients susceptible to infliximab-induced infusion reactions with hydrocortisone therapy.⁴⁸

Delayed infusion reaction is very rare (0.7% to 3%). Patients presents after 4 to 9 days with back pain, myalgia, arthralgia, and skin rash.^{46,47} It is seen after the second or third infusion dose and usually responds to corticosteroid therapy.

Infliximab therapies often induce formation of anti nuclear antibody and anti double standard antibody.⁴⁹ However these antibodies are not of any clinical significance as studies suggest that no pediatric patients have developed drug-induced systemic lupus or organ damage.

Infections

Infliximab causes decreased levels of polymorph nuclear cells and T-cell lymphocytes specifically at mucosal site. This results in increased risk of infectious with bacteria, virus and fungi. Active infection is a contraindication for infliximab use. Also, live vaccines are contraindicated as there is an increase risk of serious infection. Every patient has to undergo a screening test for tuberculosis, as multiple studies suggest reactivation of latent tuberculosis.^{50,51}

The risk of infection is 3.8% to 8% and the upper respiratory tract is commonly affected.^{26,52} In the REACH study, the incidence rate of upper respiratory tract infection was 35.8% and 32.0% in patients receiving infliximab every 8 weeks and every 12 weeks, respectively.³⁹ Overall infection rate was high (73.6%) among the first group patients than the later group (38.0%). But serious infection occurred at the same rate in both the groups (5.7% to 8%). In a study of adult patients with CD, Colombel and coworkers treated 500 patients with infliximab, 41 (8.2%) of whom developed infection. Among these 41 patients, 15 had serious infection (2 fatal sepsis, 8 pneumonia, 1 severe viral gastroenteritis, 2 abdominal abscess, 1 arm cellulitis, 1 histoplasmosis).⁵³ Other studies also suggest the occurrence of *Listeria monocytogenes* meningitis, cutaneous *Tinea*, shingles, and

herpes zoster.^{45,54} One report also suggests reactivation of hepatitis B in 3 patients diagnosed with chronic hepatitis B on treatment with infliximab.⁵⁵

Malignancy

In a prospective study of 20 patients, 28% developed reactivation of Epstein-Barr virus (EBV). However, EBV PCR level returned to normal after 6 months of discontinuing infliximab.⁵⁶ In a study of 6290 adult patients on maintenance infliximab therapy, there was no increased risk of malignancy in the infliximab group compared to patients on conventional therapy.⁵⁷ In a multi-center matched-pair trial, the incidence rate of malignancy was 2.2% (9 patients) in the CD group and 1.7% (7 patients) in the non-CD group after a follow-up of 4.5 years.⁵⁸ Meena and coworkers first reported a case of hepatosplenic T-cell lymphoma in a 17-year-old female CD patient treated with infliximab and 6-MP.²⁷ Nine more cases of hepatic T-cell lymphoma have been reported in IBD patients treated with infliximab and 6-MP/AZA.⁵⁹ However there is no case report of an IBD patient developing hepatic T-cell lymphoma on infliximab alone.

Summary

The arsenal of biological therapies is increasing. A large multi-centered pediatric study is now investigating the use of adalimumab in children with CD. Furthermore, the FDA approval of certolizumab, a novel pegylated anti-TNF therapy, is expected soon. The pediatrician will soon be faced with the dilemma of which medications to use, in either the more traditional step-up or top-down approach. Indeed, there is a growing tendency to consider biological drugs in lieu of more traditional therapies, as discussed above. While genotype-phenotype correlations may allow clinicians to predict certain more aggressive forms of CD, future studies are still needed to provide an evidenced-based approach to drug therapy.

Disclosures

Dr Cuffari is a consultant for, and receives research support from, UCB, the manufacturer of certolizumab.

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