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REVIEW

Profile of infliximab in the treatment of pediatric Crohn's disease

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Abstract: In recent years, a novel biologic therapy with monoclonal antibodies against tumor necrosis factor-alpha has revolutionized the treatment of Crohn's disease. Infliximab, the first biologic agent, has been demonstrated to considerably improve both clinical and endoscopic outcomes. In view of the growing popularity of infliximab in the management of Crohn's disease, we review the profile of the agent in the treatment of this disease in a pediatric setting.

Keywords: infliximab, Crohn's disease, children, biologic therapy, anti-TNF-agents

Introduction

Infliximab (Remicade®) is a chimeric monoclonal antibody against tumor necrosis factor-alpha (TNF-α), used to treat autoimmune and immune-mediated diseases. The drug was initially approved by the US Food and Drug Administration for the treatment of Crohn's disease (CD) in August 1998.[1] Since that time, biologic therapy with monoclonal antibodies against TNF-α has revolutionized the treatment of inflammatory bowel disease (IBD).[2,3] Clinical trials demonstrated that infliximab is efficacious in fistula closure in CD patients,[4] which resulted in its approval for the treatment of fistulizing disease.[5] Moreover, the agent was shown to induce and maintain remission in inflammatory CD;[6–8] treatment with infliximab results in considerable improvement of both clinical and endoscopic variables.[9–11] Furthermore, scheduled maintenance infliximab monotherapy was demonstrated to prevent postoperative recurrence of CD.[12]

Infliximab was first used in pediatrics in 1998, but was not approved for use in pediatric CD until 2006. Currently, the drug is licensed for the treatment of acute CD in children who do not respond to conventional therapy and in patients whose disease is associated with fistulization.[13,14] In view of the growing popularity of infliximab in the management of CD, we decided to review the profile of this agent in the treatment of CD in a pediatric setting. We also discuss the potential use of infliximab biosimilars.

TNF-α-mediated intestinal inflammation and mode of action of infliximab

TNF-α, a proinflammatory cytokine, has been shown to play an important role in the pathogenesis of CD.[15] TNF-α mediates signals between immune cells, which results in inflammation, thrombosis, and fibrinolysis. Various stimuli, including bacterial endotoxins, radiation, and viral antigens, may trigger the release of TNF-α from monocytes, macrophages, and T lymphocytes.[16] TNF-α is predominantly expressed on the intestinal mucosa and intestinal lumen in CD patients.[17] At the mucosal level, TNF-α

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is involved in recruitment of circulating inflammatory cells to the intestinal tissue and resultant development of edema. Moreover, TNF-α stimulates coagulation due to activation of thrombin, and participates in granuloma formation.[16] Therefore, the expression of this proinflammatory cytokine needs be tightly controlled, and failure to do so results in an unmediated inflammatory response. Other biological activities of TNF-α include induction of proinflammatory cytokine (eg, interleukin-1 and interleukin-6) release, enhancement of leukocyte movement or migration of these cells from the blood vessels into the tissues (by increasing the permeability of the endothelial layer of blood vessels), and stimulation of adhesion molecule release.[18]

Infliximab is a chimeric immunoglobulin G-1 monoclonal antibody with a high specificity for TNF-α. It neutralizes the biological activity of TNF-α due to high-affinity binding to the soluble (free floating in the blood) and transmembrane (expressed on the outer membranes of T-cells and similar immune cells) forms of the cytokine, and inhibits or prevents effective binding of TNF-α to its receptors.[19]

Infliximab is capable of neutralizing all forms (extracellular-bound, transmembrane-bound, and receptor-bound) of TNF-α. This function has been proven in animal studies demonstrating that inhibition of soluble TNF causes the anti-inflammatory effect, whereas blocking of its transmural forms results in increased sensitivity to infection and exacerbation of demyelination. TNF acts through its receptors (TNFRs). These receptors are either constitutively expressed (TNFR1, p55) or inducible (TNFR2, p75).[20] TNFR1 serves as the major mediator of action of TNF. This receptor can be activated by binding both forms of TNF (either soluble or transmural); however, it shows a significant preference for a soluble one. TNFR2, on the other hand, is preferentially activated by transmural TNF.[21] The expression and biologic roles of these two receptors also differ. While TNFR1 is expressed in most cell types and its function is to initiate inflammatory responses and mediate apoptosis,[22] TNFR2 expression is limited to specific cells, such as oligodendrocytes, microglia, and astrocytes in the central nervous system, endothelial cells, lymphocytes, and cardiac myocytes.[23] The function of TNFR2 is to induce antiviral immune responses through activation of cytotoxic T lymphocytes.[24]

Additionally, this anti-TNF antibody has the ability to lyse cells involved in the inflammatory process. As a result, infliximab induces apoptosis of TNF-α-producing cells, and promotes antibody-dependent and complement-dependent cytotoxicity.[25,26] The agent shows high specificity for TNF-α, and does not neutralize TNF-β (also referred to as lymphotoxin α), an unrelated cytokine that binds to different receptors than TNF-α.

Profile of pediatric patients qualifying for biologic therapy with infliximab

According to the new European Crohn's and Colitis Organization/European Society for Paediatric Gastroenterology, Hepatology, and Nutrition guidelines on clinical management of pediatric CD, infliximab is recommended for induction and maintenance of remission in children with chronically active luminal disease that did not respond to prior optimized immunomodulating therapy, as well as in patients with active steroid-refractory disease. Moreover, when combined with appropriate surgical intervention, infliximab is recommended as a primary induction and maintenance therapy for children with active perianal fistulizing disease.[27] However, the criteria for use of biologic agents for pediatrics in clinical trials vary depending on the research protocol. Also, use of these agents within reimbursed therapeutic programs is mostly determined by country health policy. In either case, the patient needs to be in a poor clinical condition, mostly defined by pediatric CD activity index (PCDAI) score, and have failed other conventional treatments.

The authors of a retrospective Scandinavian study including 36 patients with newly diagnosed CD aged <18 years investigated whether clinical, endoscopic, and biochemical factors at diagnosis were associated with early initiation of treatment with infliximab. They demonstrated that high levels of inflammatory markers and the presence of upper gastrointestinal lesions were associated with initiation of treatment with infliximab. However, a substantial proportion of patients participating in this trial still showed unspecific lesions in the upper gastrointestinal tract regardless of treatment.[28] The data from central Europe are consistent with those from Scandinavia. A Polish study of children who qualified to receive biologic therapy with infliximab showed that this group presented with a severe rather than moderate course of CD. At qualification, most of the patients were in poor clinical condition with high PCDAI values and a lack of response to other conventional treatments. However, in contrast with the Scandinavian cohort, most of the lesions were found in the ileum and colon. Extraintestinal manifestations were reported in 16.8% of the patients, with arthralgia/arthritis being the most common (77.8%). The most frequently

found complications were nutritional and growth disorders, documented in nine patients (8.4%).[29]

A distinct issue is so-called early-onset IBD, which develops during the first years of life (under the age of 5 years) and is considered to have a specific phenotype.[30] Overall, the disease manifestations are primarily colonic, with severe perianal disease and severe extragastrointestinal manifestations.[31,32]

Early-onset IBD presents with a very severe manifestation and a guarded prognosis, with life-threatening symptoms, and needs an aggressive therapeutic approach.[33] The available data point to the complexity of early-onset IBD, representing a group of distinct diseases with several pathogenetic abnormalities, as recently suggested by impaired interleukin-10 signaling.[34,35] Moreover, this early form of IBD is resistant to any kind of therapy, including biologic treatment. It has been suggested that allogeneic stem cell transplantation may result in disease remission in such patients.[36]

Infliximab for induction and maintenance of remission

Studies evaluating the safety and efficacy of infliximab in a pediatric setting showed that both response and remission rates are far superior compared with conventional therapy.[37,38] Moreover, infliximab seems to be more efficacious in children than in adults.[39,40]

Induction therapy

A multicenter, open-label, dose-blinded trial conducted by Baldassano et al demonstrated the safety and efficacy of a single infliximab infusion in pediatric patients with refractory moderate to severe CD. The clinical response and remission rates documented during a 12-week follow-up were 100% and 48%, respectively, and significant improvements in PCDAI and laboratory parameters were noted.[41] However, the approval by the US Food and Drug Administration for use of infliximab in pediatric CD was based on the results of the large and much publicized REACH study. This prospective, multicenter, randomized controlled trial included 112 children with moderately or severely active CD. The study confirmed that infliximab is effective in the induction and maintenance of remission.[42] Clinical response and clinical remission rates after a 10-week follow-up (corresponding to three doses of infliximab) were 88.4% and 58.9%, respectively. The results of the REACH study are considered a therapeutic optimum for this group of patients. The RISK trial, an observational study conducted between 2008 and 2012 at 28 pediatric gastroenterology centers in North America compared the effectiveness of early ($\leq$3 months after diagnosis) treatment with an anti-TNF-α and the therapy with an immunomodulating agent in attaining clinical remission and facilitating growth in patients $<$17 years of age with inflammatory (non-penetrating, non-stricturing) CD. The study demonstrated that early treatment with biologic agents is superior to early immunomodulating therapy (remission rates 85.3% vs 60.3%; relative risk 1.41, 95% confidence interval 1.14–1.75; P=0.0017).[43]

Maintenance therapy

Newly published data demonstrate sustained effectiveness of infliximab in children and adolescents with luminal CD.[44] A retrospective analysis of 195 pediatric patients receiving infliximab with or without an immunomodulating agent showed that the clinical response is associated with enhanced linear growth, especially if treatment is initiated early. The response was shown to be further sustained due to concomitant immunomodulation. Another prospective study of 51 children with severe CD resistant to conventional therapy documented the beneficial effects of infliximab, namely a decrease in PCDAI values and an increase in quality of life evaluated by IMPACT-III.[45] In this study, the initial IMPACT-III scores (median, percentile 25–75 at week 0: 115, 102.5–130.25) increased significantly ($P<0.001$) following biologic therapy at week 54 (median 141.5, 124.5–153.75). Clinical and laboratory parameters also improved significantly ($P<0.001$).

Moreover, this study documented a relationship between IMPACT-III scores, PCDAI values, and laboratory parameters. However, a secondary loss of response to infliximab was observed in a considerable proportion of initial responders. The rates of loss of response observed during 3–5 years of follow-up of patients participating in multicenter pediatric studies ranged between 33% and 50%.[46] A retrospective study of 185 children with luminal CD showed that the cumulative probability of a sustained response to infliximab after 1, 2, and 3 years of maintenance therapy with this agent amounts to 83%, 74%, and 70%, respectively.[47] Currently, routine therapy for children with newly diagnosed CD includes early administration of immunomodulators after initial treatment with corticosteroids. A biologic agent is only administered after failure of the other therapies. A study of the short-term and long-term benefits and safety of infliximab showed that the agent was effective in more than 50% of a population-based cohort including 120 patients diagnosed with CD at $<$17 years of age and followed up for a median of 32 months. Moreover, the long-term infliximab responders had a lower

rate of surgery and improved catch-up in growth, especially when receiving scheduled infliximab therapy.[48]

Infliximab for induction of mucosal healing

Since mucosal healing may be the only way to alter the disease course in IBD patients, according to the newly published guidelines, this parameter should be considered as the ultimate endpoint in clinical trials.[49] The ACCENT I trial showed that repeated administration of infliximab may maintain not only clinical but also endoscopic healing,[50] which seems to be associated with a longer duration of clinical remission in adult patients with CD.[51] One of the first studies on mucosal healing in a pediatric population was conducted by Kierkus et al. In this study of Polish pediatric patients with CD, induction biologic therapy with three doses of infliximab was shown to result in mucosal healing; the treatment was clinically effective in 72% of the patients and induced a remission in 33%.[9] A retrospective analysis of 33 patients diagnosed with CD at <18 years of age, including 29 children treated with infliximab and 19 receiving adalimumab, documented considerable rates of mucosal healing and clinical responses. The subsets of patients treated with infliximab and adalimumab did not differ in terms of the overall clinical response rates, and the two drugs proved to be well tolerated.[52]

Safety profile of infliximab

Safety issues are of vital importance in the pediatric setting. Although biologics are generally considered to be well tolerated and safe, follow-up data on their safety are still limited. Safety concerns associated with biologic therapies include an increased risk of infections, autoimmune conditions, lymphomas, demyelinating diseases, and exacerbation of heart failure.[53–55] Moreover, reactivation of mycobacterial infections has been reported in patients treated with anti-TNF agents.[56] The incidence of opportunistic infections in various groups of patients treated with infliximab varies between 0.3% and 0.9%,[57] and seems to be mainly associated with use of concomitant treatment with either corticosteroids or azathioprine/6-mercaptopurine.[58] Nonetheless, appropriate qualification for biologic treatment, based on a complete evaluation (including a chest X-ray and tuberculin test) and careful monitoring of potential adverse events, constitutes the best way of preventing serious complications.

Another important problem concerning safety is the vaccination issue. Although it is suggested that the response to vaccines may be reduced in CD patients receiving immunosuppressive agents, most vaccines, except for the live attenuated ones, can be safely administered to IBD patients, even those on immunosuppressants.

People with IBD, especially those on long-term immunosuppressive drugs, are at risk of contracting hepatitis B virus (HBV) infection, so HBV vaccination should be considered in these cases.[59] Furthermore, immunosuppressive medications, including anti-TNF-α agents, may lead to reactivation of HBV replication in patients with chronic HBV infection.[60,61] HBV vaccination is effective in preventing infection and consequently acute and chronic liver disease.[62]

Administration of the anti-TNF monoclonal antibodies frequently results in formation of antibodies against infliximab and adalimumab. The presence of these antibodies was shown to be associated with a shorter duration of therapeutic response and a higher incidence of infusion reactions.[63] The long-term safety of infliximab and other therapies was evaluated on the basis of data from the TREAT registry of patients with CD who were followed up prospectively.[64] A total of 6,290 patients (3,179 infliximab recipients and 3,111 recipients of other therapies) have been enrolled in this registry since August 2004. According to the available data, the overall safety profile of infliximab is similar to the profiles of conventional immunomodulatory agents.[65]

Biosimilars

Biosimilar medicinal products (biosimilars) are novel versions of previously approved biopharmaceutics, data protection for which has expired. Both the US Food and Drug Administration and the European Commission have already approved the first biosimilar of infliximab for the treatment of rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, nummular psoriasis, and IBD; the agent, CT-P13, is marketed under the brand names Remsima™ and Inflectra™. The biosimilar antibody has been tested so far mostly in patients with rheumatoid arthritis and ankylosing spondylitis, and proved to be equivalent to the original agent in terms of efficacy, safety, and pharmacokinetic profile.[66–68]

In two well-designed clinical trials,[67,68] CT-P13 was equivalent to the reference infliximab in terms of pharmacokinetic properties in patients with ankylosing spondylitis and in terms of efficacy in patients with rheumatoid arthritis. In both studies, the biosimilar was generally well tolerated with a safety profile similar to that of the reference biologic agent. Preliminary data from trial extensions demonstrated that, in patients who switched from infliximab to CT-P13, efficacy was sustained and similar to that in patients who were treated continuously with CT-P13.

However, we still do not know if the efficacy and safety data can be extrapolated to other clinical entities and whether the biosimilar and its originator can be used interchangeably. A retrospective study of patients with CD (n=8) and ulcerative colitis (n=9) who received CT-P13 between November 2012 and October 2013 demonstrated comparable outcomes to infliximab. A total of seven patients (five with ulcerative colitis and two with CD) showed a clinical response or remission at 8 weeks. One patient with CD did not respond to CT-P13. In nine patients (four with ulcerative colitis and five with CD) who received the originator as maintenance therapy, infliximab was replaced with CT-P13. CT-P13 was discontinued in one patient with ulcerative colitis due to development of arthralgia, and another patient did not respond to the biosimilar during the study period.[69] Limited preliminary data from trial extensions suggest that the outcomes in patients switched from infliximab to CT-P13 are similar to those in individuals treated continuously with the latter agent.[70] As with all biosimilar and generic agents, CT-P13 has a potential to reduce treatment costs when compared with those of infliximab, which makes it a useful alternative to its originator in patients requiring biologic therapy. However, a large, randomized, double-blind prospective trial is needed to verify if CT-P13 is really a biosimilar of infliximab in the treatment of IBD, and whether these two agents can be used interchangeably in this setting.

Conclusion

Infliximab, a biologic anti-TNF-α agent, has revolutionized the treatment of pediatric CD. According to the available data, the drug is highly effective in induction and maintenance of remission in children with a severe course of the disease. Moreover, recent data from clinical trials suggest that infliximab is also efficacious in promotion of mucosal healing. Although biologics are generally considered to be well tolerated and safe, the follow-up data on their safety are still limited. Currently, a more cost-effective alternative to infliximab has emerged, ie, biosimilar agents (Remsima/Inflectra), which seem to be equivalent to the original product in terms of efficacy, safety, and pharmacokinetic profile.

Disclosure

The author reports no conflicts of interest in this work.

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