Anti-Tumor Necrosis Factor Therapy for Pediatric Inflammatory Bowel Diseases

Yoram Bujanover MD and Batia Weiss MD

Division of Pediatric Gastroenterology and Nutrition, Safra Children's Hospital, Sheba Medical Center, Tel Hashomer, and Sackler Faculty of Medicine, Tel Aviv University, Ramat Aviv, Israel

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Crohn's disease and ulcerative colitis are chronic inflammatory bowel diseases that afflict children as well as adults. Approximately 25–35% of patients with Crohn's disease and 20% of those with ulcerative colitis are under the age of 20 [1]. These diseases affect males and females equally. Epidemiological studies have demonstrated a gradual increase in the incidence and prevalence of CD and UC in recent years in most developed countries [2].

The standard therapies for these diseases include anti-inflammatory agents like oral and rectal 5-aminosalic acid compounds, antibiotics such as metronidazole and quinolones, special nutritional formulas, immunomodulators like topical and systemic steroids, azathioprine, 6-mercaptopurine, cyclosporine and methotrexate. In addition, therapy includes antidiarrheal agents, antispasmodics, and pre- and probiotic agents [3]. The introduction of newer biological agents, namely medications that target specific molecules in the immune system, has changed the standard therapy and is beneficial to many patients.

Tumor necrosis factor-alpha antagonists are the most studied biologicals. TNF has a broad range of pro-inflammatory effects and plays a central role in the regulation of inflammation. Produced mainly in the mononuclear cells of the lamina propria, TNF has the ability to induce the secretion of pro-inflammatory cytokines and chemokines from stromal, endothelial and mucosal mononuclear cells.

Activation of nuclear factor-kappa B and intracellular transcription factors results in increased production of interleukin-1 and 6 and activation of macrophages and dentritic cells. TNF induces mucosal T cells, causing increased production of interferon-gamma and stromal cells to produce matrix metalloproteinases, which provoke the increased expression of adhesion molecules from the endothelial cells – all of which injure the mucosa, increase its permeability, enhance apoptosis and amplify the inflammatory process [4].

CD = Crohn's disease
UC = ulcerative colitis
TNF = tumor necrosis factor

Table 1. Anti-TNF biological agents

Biological agent	Anti-TNF activity	Induction of remission	Maintenance of remission
Infliximab	Chimeric IgG 1 monoclonal AB	Yes	Yes
Adalimumab	Human IgG1 monoclonal AB	Yes	Yes
Certolizumab pegol	Humanized Fab AB fragment +PEG	Yes	Yes
CDP571	Humanized IgG4	Yes	No data
Etanercept	Recombinant human fusion protein comprised of IgG1 Fc AB+ soluble p75receptors	No	No data
Onercept	Recombinant human p55 soluble receptors	No	No data

AB = antibody, PEG = polyethylene glycol
Based on data from Sands [3]

Infliximab treatment of Crohn's disease

To date six anti-TNF agents have been evaluated for the treatment of Crohn's disease [Table 1]. The one most studied is infliximab. The initial studies on the efficacy and safety of this drug were performed in adults. Infliximab is a chimeric immunoglobulin G1 antibody approved in 1998 to treat patients with moderate to severe CD who did not respond adequately to conventional therapies and to reduce the number of draining enterocutaneous fistulas. In 2002 infliximab was also approved for maintenance of remission. Treatment of adult CD patients with a single infusion of infliximab at a dose of 5 mg/kg resulted in remission after 4 weeks in 48% and 4% in the placebo group. Infusion at a dose of 10 mg/kg and 20 mg/kg resulted in a remission rate of 5% and 25% respectively [5]. There was even a higher rate of remission in patients given three induction doses administered during a period of 6 weeks. In patients with perianal disease, namely enterocutaneus fistulas, treatment with infliximab resulted in a complete closure of fistula in 58% of the patients after three infusions at 0, 2 and 6 weeks and in 19% of the placebo group. A dose of 10 mg/kg was less efficacious than 5 mg/kg [6].

The efficacy of infliximab in maintaining remission of luminal and perianal CD was also demonstrated. A single induction dose and a maintenance dose repeated every 8 weeks was effective in 24% in the infliximab group and in 9% in the placebo group at 1 year. The closure of the fistulas was achieved at 40 weeks in 58% of the patients receiving three induction doses and maintenance dose every 8 weeks. Other studies also showed that scheduled administration is more effective than episodic administrations, or as needed [7,8].

Physicians who use biological agents should be aware of the potential risk of serious infections, malignancy and immunogenicity when deciding on this type of therapy.

InflIximab therapy of pediatric CD

Infliximab treatment of pediatric Crohn's was reported initially in abstracts in 1990 [9,10] and the first article on the subject was published in 2000 [11]. In that study, Kugastan et al. examined the efficacy of infliximab in 15 consecutive children with refractory Crohn's. The study was an open-label trial of a single 5 mg/kg infliximab infusion. The efficacy measures were clinical response and clinical remission as determined by the Pediatric Crohn's Disease Activity Index. The response rate was high and the condition in 14 of 15 children (94%) improved. Ten patients achieved complete remission by 10 weeks, but 11/14 relapsed during the subsequent 52 week follow-up. The clinical response of short duration disease was maintained in 50% and of long-standing disease in none [11].

A multicenter study was performed in 2003. Twenty-one patients were enrolled in 7 study centers and were randomized to receive a single infusion of infliximab 1 mg/kg, 5 mg/kg or 10 mg/kg in an open-label dose-blinded trial. Patients were followed for 12 weeks. During the trial all 21 patients had a clinical response and 10 of the 21 achieved clinical remission during the follow-up period. The PCDAI showed a 50% improvement by week 2 and maintained 30% improvement by week 12. The 5 and 10 mg/kg doses were more effective than the 1 mg/kg dose. The same dosage effect was demonstrated in the endoscopic lesion severity score of nine patients who underwent endoscopy at week 12. Pharmacokinetic assessment performed in this study indicated that serum infliximab concentrations are proportionate to dose. Cezard and co-workers [13] reported the experience of two medical centers in France with 21 CD patients with long-standing disease who received infliximab at 0, 15 and 45 days and were followed for 12 weeks. The Harvey-Bradshaw clinical score was used to define clinical improvement or remission. In addition to the measurement of blood inflammatory markers, TNF in stool, antinuclear antibody, anti-double stranded-DNA antibody, Epstein-Barr virus serology and polymerase chain reaction were studied. The treatment was initially effective in the entire group. Nineteen patients achieved remission on day 43, and 19 of 21 patients stopped taking steroids at 3 months. A decrease in blood inflammatory markers and TNF in stool was recorded on day 45, and perianal fistula in 12 patients had closed by 3 months. However, during the follow-up period 19/21 patients experienced relapse, and 6 patients developed antinuclear antibodies that disappeared after discontinuing infliximab. Epstein-Barr virus PCR in eight patients increased significantly during treatment. Growth velocity improved in 10/21 [13].

In 2004 the French-speaking group for pediatric gastroenterology and nutrition, which included 16 centers in France, Belgium and Switzerland, reported their retrospective experience using infliximab to treat 88 children. A total of 450 infusions were administered, ranging from 1 to 17 infusions over a median time period of 4 months (range 1–17 months). Indications for treatment were active disease in 58 patients and/or fistula in 37 patients who were refractory to corticosteroid and/or other immunosuppressive agents. Efficacy was evaluated 90 ± 7 days after the first infliximab infusion in 76 patients. Symptoms subsided in 40 patients (53%), 26 patients (34%) were in remission, and 10 patients (13%) relapsed. Mean values of Harvey-Bradshaw scoring, C-reactive protein and erythrocyte sedimentation rate decreased significantly. At 90 days 24 of 43 patients (53.4%) were weaned off corticosteroids and 12 of 13 (92.3%) off parenteral nutrition. The efficacy of the treatment was not different in patients treated for active disease, for fistula, or for both. Colectomy was required in one patient [14].

The steroid-sparing effect of infliximab was also studied by Stephens' group in Philadelphia [15]. This retrospective study included 82 patients who received 432 infusions of infliximab. All the study participants except for two were also taking immunosuppressants. Length of follow-up ranged from 0 to 160 weeks. The number of infusions ranged from 1 to 18 with a median of 3. Seventy-five patients received 5 mg/kg of infliximab and 7 received 10 mg/kg. Thirty-three were receiving corticosteroids when infliximab therapy was initiated. In all, 26 patients achieved steroid independence, 9 of whom experienced relapse and resumed the steroid therapy. Three of the nine ultimately became steroid free. Nine patients required surgery after infliximab therapy.

The Pediatric Inflammatory Bowel Diseases Collaborative Research Group in the United States studied the outcomes in 109 children with Crohn's disease treated with corticosteroids. In this study short (3 months) and long (1 year) follow-up demonstrated the efficacy of infliximab treatment in steroid-resistant and dependent patients. This group comprised 24 steroid-resistant or dependent patients and 16 of them (67%) were able to discontinue steroid therapy [16].

Infliximab dependency was reported by Wewer et al [17]. During a 3 year period 24 pediatric patients with Crohn's were

PCDAI = Pediatric Crohn's Disease Activity Index

PCR = polymerase chain reaction

treated with infliximab at a dose of 5 mg/kg dose. Seven patients were treated initially with infusions at 0, 2 and 6 weeks followed by infusion on demand; 12 patients had infusions every 6 to 8 weeks, and 5 patients had infusions on demand. After 30 days of 10 infusions 8 patients (33%) achieved complete remission, 10 (42%) partial remission, 7 (29%) prolonged response, and 10 (42%) became infliximab dependent because relapse of symptoms required reinfusions to regain complete remission or prolonged response.

Infliximab therapy in Crohn's pouchitis was reported by Kooros and Katz [18]. The pediatric patients underwent colectomy because of pancolitis and an ileoanal pouch was constructed. Treatment with infliximab was initiated due to the low level of response to conventional therapy. All four patients showed a marked improvement clinically, endoscopically and histologically with repeated infliximab infusions every 8 weeks during a follow-up period of 1 year in one patient and 2 years in the other three.

Levine at al. [19] conducted a survey using an e-mail questionnaire to evaluate the management of active Crohn disease. Altogether, 167 physicians from the USA, Canada, Western Europe and Israel responded and were included in the study. Infliximab was judged to be effective for corticosteroid refractory disease by 96.4%; 17% stated that it should be used before prednisone. Infliximab was effective in maintaining remission in 40% to 83% of the participants, as reported by them.

Infliximab in pediatric ulcerative colitis

Since 2002 the treatment of 49 pediatric patients with UC has been reported. The number of patients in the four reporting centers ranged between 3 and 17, and the duration of follow-up ranged from 0.5 to 27.6 months. The short-term response in the Childrens Hospital of Philadelphia (17 patients) and John Hopkins studies was 82% and 75% respectively, and the long-term response was 63% and 66% respectively [20,21]. In those studies in which the follow-up was very short a 100% improvement was reported [22].

Therapy of IBD with other anti-TNF agents

No data are available at present on the use of the humanized IgG1 monoclonal antibody to human TNFα adalimumab in pediatric patients with CD. The data on adult CD patients demonstrate a remission rate of up to 36% at week 4 after two infusions of 160 mg/80 mg. Maintenance of remission was achieved in 94% at 24 weeks and 83% at week 56, when infusion was administered every week at a dose of 40 mg [23-25]. The results of a large maintenance trial in adult patients with CD are expected in the near future. In pediatrics the use of adolimunab was reported in patients with juvenile idiopathic arthritis.

Thalidomide inhibits TNFα through degradation of TNFα mRNA. It also inhibits IL-12 production, down-regulates integrin expression and disrupts angiogenesis. In total, 44 pediatric patients (37 with CD) in 6 studies were reported to receive thalidomide. Martelossi et al. [26] described the treatment with this agent in 23 patients with refractory IBD: 16 had a clinical response, steroid-sparing accrued in 16 of 23, and fistula closure in 2 of 3. In all six studies clinical response was achieved in 78%, and fistula closure in 66% of the patients with CD. All patients underwent sedation, and neuropathy accrued in 25% of the patients [27].

Infliximab use and immunogenicity

Infliximab is a chimeric antibody and may be associated with the formation of antibodies to infliximab, previously called human antichimeric antibodies. Detection of the antibodies depends on the sensitivity and specificity of the assay used as well as the timing of measurement. In general, it can be stated that ATI interfere with the safety and efficacy of the drug. Immunogenicity leads to clinical problems especially when infliximab is administered episodically [28].

In the episodic retreatment arm of the Accent I study [29] the cumulative incidence of ATI was 28% through 72 weeks, significantly higher than the 7–10% in patients treated with systematic treatment of 5–10 mg/kg infliximab infusion every 8 weeks. In the episodic treatment, ATI impaired the kinetics of the drug, with a more rapid reduction in serum infliximab concentrations from post-infusion peak levels, and a reduction in the magnitude and duration of clinical response. The presence of ATI was associated with a 12% increase in infusion reactions. Patients receiving immunomodulators had a lower incidence of ATI than patients not receiving immunosuppressants (16% in episodic treatment, 4–7% in systematic treatment). However, in the trial population, similar proportions of antibody-positive, negative or inconclusive patients achieved clinical response and clinical remission at 54 weeks.

In open-cohort studies of patients treated with infliximab in an episodic or "on demand" manner, the formation of ATI was found to be an important clinical problem. Baert and colleagues [30] detected ATI in 61% of patients and Farrel and team [31] reported ATI in 36% of their patients. Both studies demonstrated that the formation of ATI was associated with the occurrence of infusion reactions, lower post-infusion infliximab serum levels and a shortened duration of response. ATI formation was reduced by concomitant therapy with immunosuppressants – either azathioprine or methotrexate.

The occurrence of ATI among pediatric patients was studied in a retrospective study by Miele et al. [32]. ATI determination in 34 pediatric patients with IBD showed the presence of antibodies in 12 of 34 patients (35%). The antibody determination was made before the infximab infusion, and since antibodies might wane with time it is possible that the number of patients with ATI was underestimated. The clinical importance of ATI was the rate of infusion reactions, which occurred in 13.8% of ATI-positive patients compared with 3.6% of infusions in ATI-negative patients. The titer of ATI correlated with the risk of reaction. When the titer was higher than 8 µg/ml the relative risk for reaction was

IgG = immunoglobulin G

IBD = inflammatory bowel disease
ATI = antibodies to IFX

3.9 (confidence interval 1.3–11.7). The use of concomitant immunomodulatory agents (in 29 of 34 patients) was associated with risk reduction for ATI development (relative risk 0.34, confidence interval 0.17–0.72) and a lower ATI titer in ATI-positive patients. Young age (< 14 years) appeared to be protective against the development of ATI, and infusion interval was not associated with ATI, in contrast to reports on adults.

Anti-TNFα and other new biological agents have significant advanced inflammatory bowel disease therapy. This mode of treatment is effective and well tolerated by children and adult patients.

Several strategies to minimize the clinical impact of ATI have been suggested [33], including a three-dose induction regimen to maximize efficacy, a systematic maintenance regimen every 8 weeks to increase duration of response, and/or concomitant use of immunomodulators and/or pretreatment with high dose corticosteroids.

Safety of infliximab treatment of IBD

Infusion reactions

The most common adverse effects with infliximab are related to the formation of ATI. Acute infusion reactions have been reported to occur in a median of 14.7% of pediatric patients and 5% of infusions [27]. Clinical features of infusion reaction include shortness of breath, chest tightness, rash, flushing, fever, hypoxemia, chills, itching, and blood pressure instability. Acute infusion reactions are generally easy to manage and are treated by slowing the infusion rate and administering antipyretics, antihistamines, hydrocortisone and/or epinephrine [14,15]. Prophylactic use of antipyretics, antihistamines and corticosteroids just before each infusion has been shown to reduce the number of reactions in patients previously suffering from an infusion reaction. Jacostein et al. [34] retrospectively studied the effect of premedication prior to infliximab infusion in pediatric patients. Of 243 patients receiving infliximab, 33 took premedication prior to infusion reaction, while the remaining 210 did not take premedication until development of the first infusion reaction. Twelve of the 33 patients (36%) who received premedication before the first reaction had an infusion reaction, versus 28 of 210 patients (13%) who were not premedicated before the first reaction. The authors concluded that premedication does not seem to prevent the development of infusion reaction; however, once the reaction has occurred, premedication may be indicated to prevent the subsequent infusion reactions.

Delayed infusion reactions, also called serum sickness-like reactions, occur 2–14 days after infusion (most commonly after a drug interruption of 4–6 months or more since the last dose). The clinical features include fever, arthralgias or arthritis, and rash. Treatment is with high dose steroids for 4–7 days. Patients who suffered delayed reactions can be retreated with infliximab but need prophylaxis with high dose prednisone 2 days before and for 5–7 days post-transfusion. After a drug-free interval of more than 14 weeks, prophylaxis with hydrocortisone is recommended in all patients to avoid infusion reactions [28]. In children, delayed infusion reactions range between 0 and 2.2% [14,15]. Kugathasan et al. [35] compared the rate of systemic reactions during infliximab retreatment in adults and children and found a higher rate of severe reactions in adults than in children – 21% versus 3% respectively. No delayed systemic reactions were detected in patients younger than 17 years.

Infections

In clinical studies, 36% of patients treated with infliximab and 28% of patients treated with placebo had infections that required therapy. Respiratory tract infections were more common in patients treated with infliximab than with standard therapies [28]. The rate of serious infections in placebo-controlled clinical trials in Crohn's disease and rheumatoid arthritis patients was 6% compared to 7% in patients treated with placebo [28]. In a large cohort study of 500 patients from the Mayo Clinic, infliximab-related infections were found in 8%. Twenty patients had serious infections: 2 had fatal sepsis, 8 had pneumonia, 6 viral infections, 2 abdominal abscess, 1 cellulitis and 1 histoplasmosis [36]. Serious infections were reported in pediatric patients as well. Lamireau and co-authors [14] reported abscess formation during infliximab therapy in 3 of 82 patients, 2 of them perianal. Stephens and collaborators [15], in a study of 82 patients, encountered infections with herpes zoster in 3 patients and *Listeria monocytogenes* meningitis in one. Catheter-related sepsis, upper respiratory infections, pancreatitis, sinusitis and appendicitis in single patients were reported in other studies [12,13]. The exact rate of infections in pediatric patients treated with infliximab is not clear.

Activation of latent tuberculosis and other opportunistic infections has been associated with infliximab therapy. By February 2005, 709 cases of tuberculosis were reported, including 591 spontaneous reports, 86 trial reports and 32 registry reports. The median time from the first infiximab infusion to the onset of symptoms was 123 days. In 62 cases tuberculosis was the underlying cause of death. All patients who are candidates for treatment with an anti-TNF agent should undergo pretreatment screening for tuberculosis. The screening includes a detailed history and chest X-ray. The usefulness of a skin test for screening is debatable. There is a high rate of anergy and false negative skin tests in CD patients. Patients with positive skin tests should receive prophylactic therapy with isoniazide and pyridoxine for 6 months, and 2–4 weeks before the first infliximab infusion [28].

In children, activation of opportunistic infections such as shingles has been rarely reported [15]. An increase in EBV PCR

EBV = Epstein-Barr virus

titers was observed in pediatric patients; however, after stopping infliximab the EBV PCR became negative [13].

Vaccination schedules with inactivated viral and bacterial vaccines should be rigorously maintained. Data regarding live vaccines are lacking, but these are usually avoided in patients receiving infliximab therapy, as with all immunosuppressive therapy. Consideration should be given to obtaining measles and varicella titer before starting therapy [27].

Other systemic manifestations

Demyelinating neurological diseases have been reported rarely in adult patients. Known demyelinating disease would be a relative contraindication [27]. Known heart failure is also a relative contraindication for infliximab therapy because of reports of worsening of severe heart failure and increased mortality [37]. Mild-to-moderate increase in liver enzymes has been reported rarely. Severe hepatotoxicity has seldom been observed, and no causal relationship with infliximab was established [28].

Leukopenia and other hematological abnormalities might occur, and monitoring of complete blood count, differential and transaminases after every infliximab infusion is recommended [27].

Infliximab therapy is frequently associated with the formation of antinuclear antibodies and antibodies to double-stranded DNA. Drug-induced lupus reactions without end-organ damage rarely occur. Antinuclear antibodies are associated with female gender and with the occurrence of papulosquamous or butterfly rash. Most of the studies in children have not performed routine serological evaluation. Cezard et al [13] found antinuclear antibodies in 6 of 21 children without any clinical symptoms. These antibodies disappeared within 6 months after discontinuation of infliximab. The development of antinuclear antibodies is not an indication to discontinue therapy [28].

Risk of cancer

In the CD and rheumatoid arthritis trials, 6 lymphoma cases were diagnosed for the follow-up of 4148 patient years, versus 0 for 691 placebo patients. All lymphomas occurred in patients treated with concomitant immunosuppression. Four of these lymphomas occurred in patients with RA. In RA, the background incidence on lymphoma is increased in comparison to the general population. Data for CD are scarce, and there is lack of evidence at this stage of an increased risk of lymphoma associated with the use of infliximab in Crohn's disease [28].

A rare subtype of non-Hodgkin lymphoma, called hepatosplenic T cell lymphoma, was described in six adolescent and young adult patients with Crohn's disease; their ages ranged from 12 to 31 years and they were treated with infliximab. All patients received concomitant azathioprine or 6-mercatopurine. Five of the six patients died as a result of their lymphoma. Exposure to infliximab ranged from 1–2 infusions to approximately 4 years of maintenance therapy, and to azathioprine for more than 2 years (Company report, July 2006).

RA = rheumatoid arthritis

Mortality in patients with inflammatory bowel diseases treated with infliximab is not higher than in non-treated patients, and is primarily a consequence of disease complications [28].

Large registries such as the TREAT registry in North America and the ENCORE registry in Europe gather the data on the safety of infliximab. A preliminary analysis of 6000 in the TREAT registry shows that serious infections and mortality in CD is related especially to the use of steroids and not to the use of infliximab. The current rate of lymphoma or overall cancer was not higher in the cohort of patients treated with infliximab than in the patients treated with conventional therapy [28]. The fact that pediatric patients have immature immune systems and will possibly have a longer exposure to the biological agent may put this group at a greater risk of developing side effects and immune reactions. At present the relatively short follow-up of patients treated with infliximab does not allow us to draw clear conclusions about these safety issues.

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Correspondence: Dr. Y. Bujanover, Division of Pediatric Gastroenterology, Safra Chidren's Hospital, Sheba Medical center, Tel Hashomer 52621, Israel.
Phone: (972-3) 530-2558
Fax: (972-3) 530-2883
email: bujyoram@netvision.net.il