REVIEW ARTICLE

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Infliximab Therapy in Children and Adolescents with Inflammatory Bowel Disease

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Contents

Abstract

This review summarises the present knowledge of infliximab therapy in children with inflammatory bowel disease (IBD) based on the available published literature.

Infliximab, the chimeric monoclonal IgG_1 antibody to tumour necrosis factor-α, is indicated for medically refractory luminal and fistulising paediatric Crohn's disease. Recently, ulcerative colitis case series in children and adolescents suggested that infliximab might also be effective for treatment of ulcerative colitis resistant to standard medical therapy.

Induction therapy with infliximab 5 mg/kg at weeks 0, 2 and 6 is routinely used. Since the majority of patients will relapse if not re-treated, a long-term approach with systematic re-treatment with 5 mg/kg every 8–12 weeks is recommended. Maintenance therapy every 8 weeks was superior to 12 weeks' adminis-

tration in maintaining response and remission in the largest-to-date paediatric randomised trial. Concomitant immunosuppressive therapy reduces the risk of infliximab antibody formation and infusion reactions, and prolongs the duration of treatment success. Severe reactions may not be an absolute contraindication to future infliximab therapy. Premedication does not prevent the development of infusion reactions; however, it is indicated for prevention of subsequent infusion reactions. Adverse events and safety findings in children are comparable to those observed in adults. Latent tuberculosis needs to be screened for. Malignancy rates in paediatric patients treated with infliximab do not seem to be increased. However, newly reported cases of hepatosplenic T-cell lymphoma in young patients with IBD treated with infliximab and mercaptopurine therapy raise concern, and long-term follow-up studies are necessary to determine the true malignancy risk.

Inflammatory bowel disease (IBD) is a chronic intestinal disease characterised by a diffuse inflammation of the intestinal mucosa associated with a dysregulation of the mucosal immune system to the otherwise innocuous luminal antigens in a genetically susceptible host.[1] This enigmatic chronic intestinal inflammation may present before the age of 20 years in 25–30% of all patients with IBD. The incidence of IBD is increasing worldwide. Two prospective paediatric epidemiological studies from the US and Sweden showed the incidence for Crohn's disease is more than twice the rate of ulcerative colitis.[2,3] The incidence of Crohn's disease and ulcerative colitis in Wisconsin children was 4.56 and 2.14 (per 100 000), respectively. Hildebrand et al.[3] found a similar pattern in paediatric patients with IBD in northern Stockholm (Crohn's disease and ulcerative colitis were 4.9 and 2.2 per 100 000, respectively). At diagnosis, 7.5% of children were younger than 5 years, whereas most of the patients were ≥11 years of age (62.5%).[4]

Certain features are unique to paediatric IBD compared with adult onset disease, such as growth failure (which is present at diagnosis in 10–40% of affected children), delay in puberty and altered bone health.[5] Presenting symptoms and disease location are also different: the majority of children present with abdominal pain and pancolitis (ulcerative colitis), whereas adults tend to present most often with diarrhoea (Crohn's disease) or rectal bleeding (ulcerative colitis) and have disease restricted to the rectum or left side of the colon.[6] Children are more likely to have proximal small bowel disease complicated by stricture formation, fistulisation and the need for surgical intervention.[7] Moreover, genetic factors may be more important in paediatric (early onset) IBD compared with adult onset IBD.[8]

Differences between children and adults with IBD can also be observed in the therapeutic field. In a paediatric population studied in a controlled trial, the success rate with mercaptopurine (6-mercaptopurine) therapy was higher than generally seen in adults.[9] Only 9% of children with Crohn's disease treated with a combination of prednisone and mercaptopurine relapsed during the follow-up period of 1 year. Unfortunately, treatment with azathioprine plus mercaptopurine has a delayed onset of action (2–4 months) and can cause serious adverse effects (severe leukopenia, hepatitis and pancreatitis). Although corticosteroids are effective in reducing symptoms of active disease, harmful side effects and lack of efficacy in maintenance therapy make this drug undesirable for long-term use. Therefore, a great need exists to develop treatment regimens that allow rapid control of active disease and then long-term maintenance of this clinical benefit.[10] Treatment with infliximab, a chimeric monoclonal antibody that binds and neutralises tumour necrosis factor (TNF)-α, represents an important step forward in fulfilling this goal.[11,12] The introduction of infliximab has greatly improved the treatment options in adult patients with IBD,[13] but less experience has been reported with paediatric patients. Nevertheless, in the last few years several trials in children with IBD treated with infliximab

have been published,[14] including the first randomised, controlled study.[15]

This review of infliximab treatment in paediatric patients with IBD summarises the present knowledge of infliximab therapy in children and adolescents with IBD, and proposes practical strategies for the administration of infliximab based on available published literature. A MEDLINE search of English literature was performed up to March 2007.

1. Mechanism of Action

TNFα is a key proinflammatory cytokine in chronic inflammatory conditions such as Crohn's disease, rheumatoid arthritis, spondyloarthropathy and psoriasis. TNFα is first produced as a 26-kD transmembrane protein with an intracellular tail that is cleaved by metalloproteinase TNFα converting enzyme (TACE) and secreted as a 17kD soluble protein.[16] Three fragments aggregate to the 51kD homotrimer complex which interacts with a pair of TNF receptors on the cellular membrane of the target cell. The receptors are called p55 TNF receptor 1 and p75 TNF receptor 2, and cross-linking of the two receptors initiates biological action.[17] TNFα is produced mainly by activated T cells and macrophages. It induces acute phase reactants, proinflammatory cytokines such as interleukin (IL)-1 and IL-6, metalloproteinases, enhances leukocyte migration and inhibits apoptosis of inflammatory cells.[18]

TNFα secreting cells are increased in the intestinal mucosa of children with Crohn's disease.[19] Faecal TNFα levels are raised in samples from children with active IBD, but there is constant low grade production of TNFα in the intestine of healthy people as well.[20] High expression of TNFα was found in the mucosa of patients with ulcerative colitis, which may explain the therapeutic efficacy of anti-TNFα administration in ulcerative colitis.[21]

Infliximab is a chimeric IgG_1 monoclonal antibody consisting of 75% human and 25% murine sequences binding specifically to human TNFα.[22] It is composed of human constant and murine variable regions. Infliximab has a serum half-life of 9.5 days and is still detectable in serum 8 weeks after infusion. Clearance of infliximab from the circulation is 9.8 mL/h.[23] At week 12, infliximab is no longer detectable with the 5 mg/kg dose, but therapeutic concentrations are maintained for a longer period with a higher dose (10 mg/kg).[24]

The mechanism of action of infliximab is not fully understood. Infliximab binds soluble bioactive TNFα and neutralises its effect. Nevertheless, this neutralisation of soluble TNF might not be enough in IBD since drugs like p55 receptor (onercept) and p75 fusion protein (etanercept), which bind TNFα efficiently, do not have therapeutic effect in IBD.[25] Binding of infliximab to membrane-bound TNF on activated T cells has been shown to induce T-cell apoptosis.[26,27] *In vivo*, monocyte apoptosis could be shown 4 hours after infliximab administration. Van den Brande et al.[28] demonstrated that in contrast to etanercept, infliximab induced apoptosis by activation of caspase 3 in peripheral blood and lamina propria T cells. Apoptotic activity may be particularly important for the long-term clinical effects of infliximab: in patients with Crohn's disease, infliximab treatment induced a sustained lamina propria T-cell apoptosis, still evident 4 weeks after the last infusion.[29] These findings demonstrate that sustained pro-apoptotic activity of infliximab extends far beyond its circulating half-life (9.5 days), and may be responsible for the prolonged remission in patients with Crohn's disease after infliximab retreatment. However, anti-TNFα molecules that do not induce apoptosis such as CDP571, a humanised anti-TNF antibody, showed promise in the treatment of Crohn's disease.[30] A single dose of CDP571 (10 mg/kg) administered in 20 paediatric patients with Crohn's disease in a 12-week open-label study was well tolerated, showing clinical efficacy in 65% of patients at week 2.[31]

Moreover, infliximab binds to membrane-bound TNFα and leads to the destruction of immune cells by antibody-dependent cellular toxicity.[32] In contrast, Shen et al. used a human-mouse chimeric model to demonstrate the effect of infliximab *in vivo*, finding that this effect was independent of Fcγ-R binding or complement activation, indicating that the contribution of antibody- and complement-dependent cellular cytotoxicity to the elimination of inflammatory cells may be very limited.[33] This group also verified caspase-dependent apoptosis of T cells and lymphocytes as the main therapeutic effect of infliximab. They showed that not only

Table I. Characteristics of different biological tumour necrosis factor (TNF)-α antagonists used in patients with inflammatory bowel disease (IBD)

Drug	Type	Administration route	Effective?
Infliximab	Chimeric IgG_1 monoclonal antibody comprising 75% human and 25% murine sequences	Intravenous	Yes
CDP571	Humanised IgG_4 antibody	Intravenous	No
Certolizumab pegol (CDP870)	Humanised TNFα Fab monoclonal antibody fragment linked to polyethylene glycol	Subcutaneous	Yes
Delmitide (RDP58)	Decapeptide blocks TNF at post-transcriptional level	Oral	Yes (?)
Etanercept	Fusion peptide, p75 TNF (R2) receptor is formulated into a dimer with Fc portion of IgG_1	Subcutaneous	No
Onercept	Fully human recombinant soluble TNF p55 receptor	Subcutaneous	No
Adalimumab	Fully human IgG_1 monoclonal antibody	Subcutaneous	Yes

infliximab, but also adalimumab (the human monoclonal antibody to TNF), induces programmed cell death of human monocytes.[34] Characteristics of different biological TNF antagonists administered in patients with IBD are summarised in table I.

More recently, a novel therapeutic effect of infliximab was described. In addition to neutralising TNFα and inducing T-cell apoptosis, infliximab inhibited the vascular inflammation in the gut.[35] Since the CD40/CD40 ligand pathway and vascular adhesion molecules (VCAM)-1 are involved in the pathogenesis of IBD, and infliximab treatment significantly reduces plasma-soluble CD40 levels and eliminates CD40 and VCAM-1 from mucosal microvessels in inflamed lamina propria in patients with Crohn's disease, this added beneficial therapeutic effect might further explain its efficacy. Finally, an additional therapeutic effect of infliximab is to normalise the abnormal intestinal permeability in Crohn's disease. Patients with active Crohn's disease given infliximab were shown to have significantly decreased intestinal permeability and disease activity 4 weeks after infusion.[36] The mechanisms of action of infliximab are summarised in figure 1.

2. Infliximab Therapy

2.1 Luminal Crohn's Disease

The first patient with Crohn's disease to receive infliximab was a 13-year-old girl with refractory colitis and perianal disease.[37] Fourteen months after the diagnosis, and after no response to azathioprine and corticosteroids, two 10 mg/kg infusions 2 weeks apart were given and she was in remission for 3 months. Infliximab was approved for the treatment of Crohn's disease in the US in 1998 and the paediatric approval for the same indication occurred in May 2006.

2.1.1 Adult Studies

The first randomised, single-dose, placebo-controlled trial in adult patients (n = 108) was published in 1997.[38] The highest response rate was observed in patients treated with 5 mg/kg (81%). One-third of patients achieved remission versus 4% for placebo, and without repeated therapy 37% of patients relapsed by 12 weeks. These results were later confirmed in several trials including the ACCENT I (A Crohn's disease Clinical trial Evaluating infliximab in a New long-term Treatment regimen) study, in which 573 patients received infliximab 5 mg/kg at week 0.[39] After assessment of response at week 2

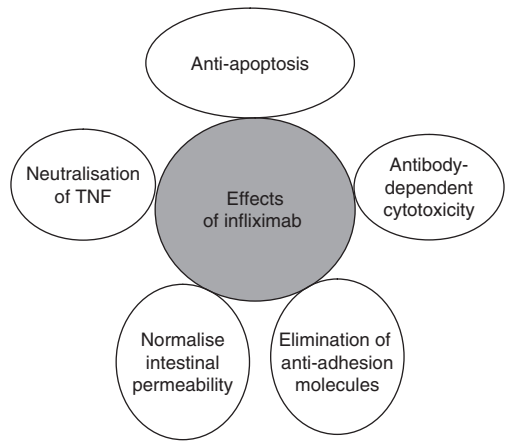

Fig. 1. Mechanisms of action of infliximab. **TNF** = tumour necrosis factor.

Table II. Patients achieving clinical response and clinical remission at different doses of a single infliximab infusion (reproduced from Baldassano et al.,[41] with permission from Blackwell Publishing)

Response	Infliximab			
	1 mg/kg; n (%) [n = 6]	5 mg/kg; n (%) [n = 7]	10 mg/kg; n (%) [n = 8]	All patients; n (%) [n= 21]
Clinical remission				
Week 4	1/6 (17)	1/6 (17)	3/6 (50)	5/18 (28)
Week 8	1/5 (20)	1/5 (20)	4/8 (50)	6/18 (33)
Week 12	0/4 (0)	1/7 (14)	2/7 (29)	3/18 (17)
Clinical response				
Week 4	5/6 (83)	6/6 (100)	4/6 (67)	15/18 (83)
Week 8	3/5 (60)	4/5 (80)	5/8 (62.5)	12/18 (67)
Week 12	3/4 (75)	3/7 (43)	5/7 (71)	11/18 (61)

(58% of patients responded to this single infusion), patients were randomly assigned to repeat administration of placebo at weeks 2 and 6 and then every 8 weeks (group I), repeat infusions of infliximab 5 mg/kg at the same time points (group II), or infliximab 5 mg/kg at weeks 2 and 6 followed by 10 mg/kg (group III). At week 30, 21% of group I patients were in remission, compared with 39% of group II and 45% of group III patients. Patients in groups II and III were more likely to have clinical remission than patients in group I (odds ratio [OR] 2.7; 95% CI 1.6, 4.6). The efficacy of scheduled infliximab therapy was better than episodic treatment in a subsequent study in which the same patients treated with infliximab in ACCENT I had participated.[40] Moreover, scheduled strategy patients had fewer IBD-related hospitalisations and surgeries, higher rates of mucosal healing, and fewer developed antibodies than episodic strategy patients.

2.1.2 Paediatric Studies

The success of infliximab therapy in adults prompted evaluation of this biological agent in children with refractory Crohn's disease. The first multicentre, open-label, dose-blinded trial in children with Crohn's disease was completed in 1998.[41] A total of 21 paediatric patients were divided in three groups and received a single infusion of infliximab 1 mg/kg (n = 6), 5 mg/kg (n = 7) or 10 mg/kg (n = 8). Clinical response was defined as improvement from baseline ≥10 points on the Pediatric Crohn's Disease Activity Index (PCDAI) or of ≥70 points on the modified Crohn's Disease Activity Index (CDAI). Clinical remission was defined as a PCDAI <10 or modified CDAI <150. During the study, all 21 patients achieved clinical response and 10 patients (48%) were in remission at some point during the observation period. The overall rate of remission was 38%. The proportion of patients achieving clinical response and clinical remission are summarised in table II. Almost all patients showed clinical response by week 1 (19/20 patients). At the 8-week evaluation visit, the proportion of patients responding was 60% for the group receiving 1 mg/kg, 80% for 5 mg/kg and 62.5% for 10 mg/kg, with a total overall response rate of 67%. The proportion of patients in remission at 8 weeks was 20% for 1 mg/kg and 5 mg/kg, and 50% for 10 mg/kg, with a total overall remission rate of 33%. Taken together, the 5 and 10 mg/kg infliximab doses were more effective than the 1 mg/kg dose in achieving clinical remission, but this remission rate was only 14% and 29% at the 12-week evaluation visit for the 5 and 10 mg/kg infliximab doses, respectively. There were no infusion reactions in any of the treatment arms.

In the same study, nine patients were endoscopically examined before and 4 weeks after infliximab administration. The median improvement in endoscopic lesion severity scores was 7%, 69% and 52% in the infliximab 1, 5 and 10 mg/kg groups, respectively. Results of pharmacokinetic assessment indicated that serum infliximab concentrations in paediatric patients were similar to those in adults. Serum infliximab concentrations were detectable through week 4 in the 1 mg/kg group, week 8 in the 5 mg/kg group and week 12 in the 10 mg/kg group.

A prospective, open-labelled trial of 15 children with medically refractory Crohn's disease was published by Kugathasan et al.[42] in 2000. Patients

received a single intravenous infusion of infliximab 5 mg/kg. By 4-weeks after infusion, 93% (14/15) had a significant decrease of both PCDAI and daily corticosteroid use, and 27% of patients (4/15) achieved clinical remission (PCDAI score ≤15). Ten patients (67%) achieved complete remission by 10 weeks. During the subsequent 52-week follow-up, among the 14 patients who initially responded to infliximab, 11 (78%) had clinical relapse that required additional medical or surgical treatment. However, among the 14 patients who responded, three of six children with early disease maintained clinical response, compared with none of eight children with late disease, indicating prolonged duration of response (12-month period) after infliximab therapy in children with early (<2 years' duration) compared with late Crohn's disease.[43]

Another open-labelled retrospective case series of 19 children who received one to three infusions of infliximab (5 mg/kg/dose) over a 12-week period for corticosteroid-resistant (7 patients) or corticosteroid-dependent disease (12 patients) showed similar results.[44] Significant decreases in the mean PCDAI (mean ± SD, 42.1 ± 13.7 to 10.0 ± 5.6; $p < 0.0001$) and mean daily prednisone dosage (baseline, 4 weeks and 12 weeks, 28 ± 14mg, 20 ± 12mg and 8 ± 12mg, respectively; $p < 0.01$) were observed. Disease activity (Physicians' Global Assessment) of the study population at the end of the follow-up period showed inactive disease in three, mild disease in nine and moderate in four patients. Three patients subsequently had surgery despite initial improvement (for stricture, perianal fistula and corticosteroid dependence). Self-limited adverse effects were noted in three children during infusion (one each of dyspnoea, facial swelling and rash).

After infliximab became available in January 2000 in France, 21 children (mean 15 years, range 11–17 years) with severe Crohn's disease were treated with infliximab 5 mg/kg on days 0, 15 and 45 in two paediatric gastroenterology units in Paris.[45] The symptoms of all patients treated with infliximab improved after two infusions. The Harvey-Bradshow index decreased significantly from 8 ± 3 on day 0 to 1 ± 2 on day 45 and 3 ± 1.9 after 3 months. Relapse rate and duration of remission in patients with early (<2 years) and late Crohn's disease were similar, contrary to a previous report.[42] Corticosteroid dose was decreased significantly at 3 months and 14 patients discontinued its use. Twelve children had perianal fistulae that were closed at 3 months. These clinical results were confirmed by a significant decrease in TNFα in stool samples and increase in serum albumin levels. Erythrocyte sedimentation rate decreased to one-third of baseline levels. Additionally, the growth velocities of ten children who had not finished pubertal growth were measured. The Z score was significantly greater after infliximab treatment (+0.5 SD) than in the year before treatment (−0.45 SD). During the follow-up period of 12 months, 90% of patients relapsed, despite continuing immunosuppressive therapy in all of them.

Beneficial clinical efficacy of infliximab, including mucosal healing and corticosteroid-sparing effect, has been confirmed by Borrelli et al.[46] In this study, 18 patients (median age 13 years, range 6–18) received three infliximab infusions (5 mg/kg at 0, 2 and 6 weeks). After 8 weeks of therapy there was a significant improvement in PCDAI, in nutritional and inflammatory blood parameters, as well as in endoscopic and histological scores. At the 8-week evaluation, 10 patients (56%) were in clinical remission (PCDAI ≤10). In all patients, corticosteroids were stopped within 4 weeks after beginning infliximab. After the initial three infusions, eight patients (44%) received re-treatment infliximab infusions (5 mg/kg) on an 8-week basis. After 6 months of therapy, PCDAI was significantly lower in patients on the re-treatment schedule than in those who received only three infliximab infusions. Moreover, a significant increase in both weight and height Z scores was observed 6 months after the initial three infusions. Weight and height gain was significantly higher in patients on re-treatment rather than in those only treated with three baseline infusions. Mild infusion reactions controlled by slowing the infusion rate were observed in four patients. No delayed-type hypersensitivity reactions were noted.

Results of infliximab induction therapy conducted in children and adolescents are depicted in table III. Additional studies showed excellent early response, with even better remission rates using repeated infliximab administration.[45,46]

It should be noted that it is somewhat difficult to compare different studies, even with the similar

Table III. Infliximab administration (induction therapy) in luminal Crohn's disease in children and adolescents

Study	No. of patients	Age (years; mean)	Early remission (duration) [response]	Prolonged remission (duration)	Dose and use of infliximab
Baldassano et al.[41]	21	8–17	28%[a] (4wk) [83%]	17%[a] (12wk)	Single; 1, 5 and 10 mg/kg
Kugathasan et al.[42]	15	6–18	27% (4wk) [94%]	67% (10wk)	Single; 5 mg/kg
Hyams et al.[44]	19	9–19 (14.4)	47% (4wk) [100%]	Inactive and mild, 52%; inactive, 21% (12wk)	1–3×; 5 mg/kg
Cezard et al.[45]	21	11–17 (15)	90% (6.5wk)	76% (12wk)	5 mg/kg on days 0, 15 and 45
Borrelli et al.[46]	18	6–18 (13)		56% (8wk)	5 mg/kg on weeks 0, 2 and 6

a Average.

number of patients and baseline characteristics because of different infusion schedules.[41,45] For example, remission rates in these two prospective paediatric trials were markedly different, with nearly 50% remission reported by one and 90% remission (at 45 days) reported by the other. One group evaluated a single infusion at different doses (1, 5 or 10 mg/kg), whereas the study from Paris was based on three consecutive same-dose infusions.

Infliximab was also effective in the treatment of paediatric patients with Crohn's pouchitis who were refractory to conventional therapies. Kooros and Katz[47] reported four patients (mean age 15.4, range 11–18 years) initially diagnosed with ulcerative colitis who underwent total colectomy with ileal pouch anal anastomosis. All patients developed chronic refractory pouchitis and were subsequently diagnosed as having Crohn's disease. After failure to respond to conventional therapy, all patients received infliximab infusions (5 mg/kg) at weeks 0, 2 and 6, and subsequently at 8-week intervals in combination with immunomodulators. All four patients showed significant clinical, endoscopic and histological improvement.

In conclusion, infliximab was efficacious in children with severe Crohn's disease; however, its beneficial effect was transitory for most patients (78–90%), with frequent relapses despite continuous administration of immunomodulators (table IV). This high rate of failure is indicative of a need for retreatment every 8 weeks as suggested for adults. It seemed earlier that children with early Crohn's disease have a better chance of prolonged response to infliximab than children with longstanding Crohn's disease, but larger paediatric multicentre studies failed to prove this association.

2.1.3 Luminal Paediatric Crohn's Disease: Long-Term Follow-Up

The efficacy of infliximab in maintenance therapy has been well documented in adults, but only a few paediatric studies have been published concerning its long-term effects.[48] The first analysis of long-term follow-up to observe the efficacy and safety of repeated use of infliximab was published by de Ridder et al.[49] In this retrospective multicentre study of the Dutch Pediatric Gastroenterology Society, the outcome of 30 patients (aged 7–18 years) with refractory Crohn's disease was analysed. Thirteen patients had active luminal disease (without fistula), 16 had resistant disease with draining fistulas and one had metastatic Crohn's disease. After a mean follow-up of 2 years (25.3 months), infliximab was effective in 53% of patients. Six patients (46%) had sustained good response after a mean period of 20 months. Two out of six patients achieved prolonged clinical remission, thus infliximab therapy was discontinued. It is of interest that one of these two patients treated early in the course

Table IV. Relapse rate after single or multiple doses of infliximab 5 mg/kg (induction therapy) in prospective trials in children and adolescents with Crohn's disease

Study	No. of patients	Infliximab 5 mg/kg	Relapse rate (%)		
			3mo	6mo	12mo
Baldassano et al.[41]	21	Single	83		
Kugathasan et al.[42]	15	Single	33 (10wk)		78
Cezard et al.[45]	21	Multiple (0, 15, 45 days)	24	53	90

of disease (11 months after diagnosis) remained in long-term remission after single infliximab infusion. The other four patients with prolonged response were given infliximab every 8 weeks unless there was evidence of relapse, after which the interval was shortened to sustain remission. Seven of 13 refractory patients had no clinical improvement after repeated infliximab infusions, thus the therapy was stopped. Five of these seven patients underwent total or subtotal colectomy.

One limitation of the interpretation of this study is its retrospective character. In some children, infliximab was discontinued after a successful induction schedule and administered at relapse after a variable period since the first use. Therefore, the long-term outcome of scheduled infliximab treatment at that time remained somewhat unclear.[50] The authors proposed that children who remain in remission for 1 year with infliximab re-treatment would remain responders to this therapy later on.

A retrospective study by Lionetti et al. showed that response to infliximab was related to disease duration in children with therapy-resistant Crohn's disease.[51] Twenty-two children and adolescents were treated with a total of 73 infusions with a range of follow-up from 18 weeks to 2.5 years. Significant improvement was noted in all patients after the initial infusion, but at 18 weeks the mean PCDAI was 5.5 ± 3 and 18.1 ± 14 in children with early Crohn's disease (duration <1 year) and long-standing Crohn's disease (duration >1 year), respectively. During the follow-up period, patients with long-standing Crohn's disease, subsequent to the initial 18 weeks, generally relapsed 2–4 months after every infliximab infusion.[51] However, a large paediatric multicentre study reported that the duration of disease did not influence the response.[52] This retrospective study included 88 children with refractory Crohn's disease (37 patients with fistula) receiving 1–17 infliximab (median 4) infusions of 5 mg/kg. At day 90 after the first infusion, symptoms improved in 49% of patients, whereas 29% of patients were in remission (Harvey-Bradshow scoring ≤4). From day 0 to 90, the dosage of corticosteroids decreased from 0.59 down to 0.17 mg/kg/day, moreover, more than half of the patients (53%) were weaned off the corticosteroids and 92% off parenteral nutrition. As mentioned, this study failed to prove the previous finding that a prolonged response is more likely in early compared with late Crohn's disease after infliximab infusion.

The National Danish Crohn's Colitis Database was used to identify all paediatric patients who received infliximab treatment in Denmark.[53] During a 3-year period, infliximab 5 mg/kg was administered to 24 patients (median age 15.4, range 9.8–18.6 years) with Crohn's disease with a median number of six infusions (range 2–11). Immediate response was determined at day 30, where 33% of patients achieved complete response, 25% had no response and the rest (42%) had partial response. Long-term response was defined as day 90, when 30% of patients achieved prolonged response, 26% had no response, and 44% became infliximab dependent. The term 'infliximab dependency' was coined as an analogue term to corticosteroid dependency, for patients needing further infliximab infusions to maintain the initial response. Six patients (25%) needed surgery during or after infliximab treatment.

Data from the most recent paediatric cohort confirmed previously published data showing a high rate of clinical remission (96%), and a high rate of relapse (96%) after infliximab induction therapy, despite maintenance of immunosuppressant therapy with a loss of response to infliximab re-treatment in 36% of children.[54]

REACH (Randomised, multicenter, open-label study to Evaluate the safety and efficacy of Anti-TNF-α CHimeric monoclonal antibody in pediatric subjects with moderately-to-severe active Crohn disease) was the first prospective, randomised study to evaluate infliximab maintenance therapy in children.[15] At baseline, 112 patients (PCDA >30) received infliximab 5 mg/kg at weeks 0, 2 and 6. The median age was 13 years and median duration of disease was 1.6 years. Patients responding to therapy at week 10 were randomised to receive infliximab 5 mg/kg every 8 weeks or every 12 weeks through week 46, and followed through week 54. Patients who lost response to 5 mg/kg every 8 weeks were crossed over to 10 mg/kg at the same interval, and patients who lost response to 5 mg/kg with the 12-week interval crossed over to 5 or 10 mg/kg every 8 weeks depending whether they lost response before or after 8 weeks, respectively. At week 10,

88% of patients (99/112) responded to infliximab and 59% of patients (66/112) achieved clinical remission. Clinical response was defined as a decrease from baseline in the PCDAI score >15 points and a total score <30, and clinical remission was defined as a PCDAI score <10 points. At week 54, 63.5% (33/52) and 56% (29/52) of patients receiving infliximab every 8 weeks showed clinical response and clinical remission, respectively, compared with 33% (17/51) and 23.5% (12/51) patients receiving treatment every 12 weeks ($p = 0.002$ and $p < 0.001$, respectively). The clinical response rates were similar regardless of age (age <13 vs >13 years), disease duration (<1 vs >1 year), and location of disease (small intestine vs colon). Thirty-five (34%) patients crossed over because of lost response during the study period, nearly half of the patients (25/51) in the 12 weeks' maintenance regimen compared with <20% (10/52) in the 8-week maintenance regimen. Four patients in each of the maintenance groups did not regain response following crossover. Adverse events and serious adverse events, including serious infections, were comparable among patients treated with infliximab every 8 weeks versus patients treated every 12 weeks.

No deaths, malignancies, tuberculosis, neurological or autoimmune disorders were noted in REACH. Infections were seen more commonly on the 8-week regimen (74% vs 38%). Serious adverse events were seen in 20% of patients, including pneumonia, abscesses and herpes zoster infection. Adverse events leading to discontinuation of the medication were seen in two patients with the 8-week regimen and 4 patients with the 12-week regimen. Antibodies to infliximab were detected in three patients, anaphylactic reactions in two patients and 18 patients experienced infusion reaction (nine in each regimen).

In conclusion, the REACH trial demonstrated that maintenance therapy with infliximab in children every 8 weeks was superior to the 12-week dose in maintaining response and remission. Adverse events and safety findings in children were comparable to those observed in adults.

2.2 Fistulising Crohn's Disease

2.2.1 Adult Studies

In adults, the results of the first placebo-controlled trial conducted in 94 patients with enterocutaneous fistulas treated with a series of three infusions of infliximab 5 or 10 mg/kg at weeks 0, 2 and 6 were presented by Present et al.[55] Fifty-five percent of the patients who received 5 mg/kg and 38% of those who received 10 mg/kg achieved closure of all fistulas. The complete response rate in the placebo group was 13%. The median length of time during which the fistulas remained closed, without re-treatment, was 3 months.

In the ACCENT II study, 69% of adult patients who responded to a loading dose of 5 mg/kg at weeks 0, 2 and 6 were randomised at 14 weeks to receive infliximab infusions (5 mg/kg every 8 weeks) or placebo through 46 weeks.[56] At week 54, 36% of patients in the infliximab maintenance group had a complete absence of draining fistulas compared with 19% of patients receiving placebo. Patients in this study who responded to induction therapy and then received maintenance therapy had fewer hospitalisations (11 vs 31 events per 100 patients) and underwent significantly fewer surgical procedures (65 vs 126 events per 100 patients) than patients receiving placebo.[57] Moreover, long-term maintenance infliximab therapy did not increase abscess development in fistulising Crohn's disease compared with placebo-treated patients (15% vs 19%, respectively).[58] A sub-analysis of the ACCENT II study showed some evidence for closure of rectovaginal fistulas in 25 women (27 draining fistulas at baseline) after infliximab treatment.[59] These data suggest that infliximab treatment also changes the long-term course of fistulising Crohn's disease, at least in adults. Unfortunately, infliximab treatment was not effective in the management of internal fistulas in four adult patients with Crohn's disease.[60] It is of interest that local injections of infliximab (20mg) along the fistula track were an effective treatment of perianal fistulas in a small number of patients with Crohn's disease.[61]

2.2.2 Paediatric Studies

Reports on fistula treatment with infliximab in children with Crohn's disease are restricted to case reports[62,63] and small case series.[64]

The response to infliximab treatment in 13 children and adolescents with fistulas was analysed in a study from Florence, Italy.[51] At 18 weeks after the initial infliximab infusion, 7 of 13 patients (54%) had complete closure, 3 of 13 (23%) had partial response and 3 of 13 (23%) had minimal response to treatment. At the same time, complete response to fistula treatment was observed in five of six children (83%) with early Crohn's disease and in two of seven (29%) with long-standing Crohn's disease. In an other prospective study, Cezard et al.[45] reported on 12 children with perianal fistulas that were closed at 3 months after repeated infliximab treatment (5 mg/kg on days 0, 15 and 45). Analysis of fistula closure in children with Crohn's disease from the Netherlands showed that 9 of 16 patients (56%) treated with infliximab had good clinical response with closure or drainage cessation.[49] Five patients did not respond to infliximab and two patients underwent colectomy after infliximab failure. One of these two died of sepsis and this is discussed in section 3.2.

Healing of the fistula tracks during infliximab therapy has been studied with magnetic resonance imaging.[65,66] These studies demonstrated that despite closure of draining external orifices after infliximab therapy, fistula tracks persist with varying degrees of residual inflammation, which may cause recurrent fistulas and pelvic abscesses during therapy. An examination under anaesthesia by a surgeon could help to solve this problem, especially in patients with complex fistulas, allowing complete inspection of the fistula as well as incision and drainage of an abscess and placement of a seton. Regueiro and Mardini[67] compared treatment of perianal fistulising Crohn's disease with infliximab alone or as an adjunct to examination under anaesthesia with seton placement. Thirty-two paediatric patients with perianal fistulising Crohn's disease who completed at least three infusions with infliximab (5 mg/kg at 0, 2 and 6 weeks) were examined.[67] Patients who had an examination under anaesthesia prior to infliximab infusions had a significantly better initial response (100% vs 83%), lower recurrence rate (44% vs 79%) and longer time to recurrence (13.5 months vs 3.6 months) compared with patients receiving infliximab alone.

In conclusion, although the number of patients in paediatric studies is too small to draw evidence-based conclusions, these data suggest that the efficacy of infliximab in healing fistulas that complicate Crohn's disease is similar to that observed in adults.

2.3 Ulcerative Colitis

2.3.1 Adult Studies

In Crohn's disease, the inflammatory response is characterised by T helper (T_h)-1 cell cytokines (TNFα, interferon [IFN]-γ, IL-12), whereas in ulcerative colitis it is characterised by the presence of T_h2 cell cytokines (IL-5, IL-13). Nevertheless, TNFα and IFNγ are also present in the intestinal mucosa of patients with ulcerative colitis. These findings initiated the use of infliximab in trials of patients with ulcerative colitis, which showed conflicting results.[68-71] Conclusive evidence for the efficacy of infliximab in the treatment of ulcerative colitis was published recently by Rutgeerts et al.[72] This paper describes the results of ACT (Active Ulcerative Colitis Trial) 1 and 2, two randomised, double-blind, placebo-controlled studies that evaluated the efficacy of infliximab for induction and maintenance therapy in adults with ulcerative colitis. In each study, 364 patients with moderate to severe active ulcerative colitis received infliximab (5mg or 10 mg/kg) or placebo at weeks 0, 2 and 6 and then every 8 weeks through week 46 (ACT 1) or week 22 (ACT 2). Patients were followed for 54 weeks in ACT 1 and 30 weeks in ACT 2. In ACT 1, 69% of patients who received 5 mg/kg and 61% of those who received 10 mg/kg had a clinical response at week 8, compared with 37% placebo recipients. In ACT 2, 64% of patients who received 5 mg/kg and 69% of those who received 10 mg/kg had a clinical response at week 8, compared with 29% of placebo recipients.

Infliximab was also effective as a rescue therapy, to avoid colectomy, in a placebo-controlled pilot study. Jarnerot et al.[73] found that 71% of adult patients with therapy-resistant ulcerative colitis avoided colectomy when treated with infliximab vs 33% of the patients given placebo (OR 4.9; 95% CI 1.4, 17).

Most recently, seven randomised controlled trials analysed patients with active ulcerative colitis who

received infliximab.[74] In adult patients with moderate to severe refractory ulcerative colitis, infliximab (three infusions at 0, 2 and 6 weeks) was more effective than placebo in inducing clinical remission (relative risk [RR] 3.22; 95% CI 2.18, 4.76), endoscopic remission (RR 1.88; 95% CI 1.54, 2.28) and clinical response (RR 1.99; 95% CI 1.65, 2.41) at 8 weeks. A single infusion of infliximab was also more effective than placebo to avoid colectomy within 90 days after infliximab administration (RR 0.44; 95% CI 0.22, 0.87).

2.3.2 Paediatric Studies

In 2005, infliximab therapy was approved in the US in adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to conventional therapy. Although this medication is not yet approved for paediatric ulcerative colitis in the US, the current most common practice is similar to the approach in adults, where it is used mainly in patients with disease refractory to conventional therapies. In this context, we reported a case series in which infliximab treatment was associated with short- and long-term success in children and adolescents with moderate to severe ulcerative colitis. Seven of nine patients (77%) with moderate to severe ulcerative colitis resistant to conventional therapy, responded to infliximab therapy. Corticosteroid therapy was discontinued in 67% of patients (six of nine).[75] During a follow-up of these patients for a minimum of 2 years, a total of 73 infliximab infusions were administered.[76] Two out of the seven responders to the initial dose of infliximab became nonresponders and underwent colectomy. Of the remaining five patients with prolonged response, two continued to receive infliximab and three were able to discontinue its use. Eight additional patients with conventional therapy-resistant ulcerative colitis were treated with infliximab, showing an 88% response rate. In summary, a short-term improvement was seen in 14 of 17 patients (82%) and prolonged improvement in 10 of 16 patients (63%) followed for at least 9 months. All five patients with severe or fulminant ulcerative colitis unresponsive to 2-week intravenous corticosteroid therapy responded and avoided colectomy.

In another retrospective study, Eidelwein et al.[77] reported on 12 paediatric patients with ulcerative colitis who received infliximab for treatment of fulminant colitis (three patients), acute exacerbation of colitis (three), corticosteroid-dependent colitis (five) and corticosteroid-refractory colitis (one). Nine patients had a complete short-term response and three had partial improvement. Eight patients had a long-term response with a median follow-up time of 10 months. Patients receiving mercaptopurine as concomitant therapy had a better response to infliximab.

Other small-sized paediatric studies using infliximab in ulcerative colitis showed similar results, with a better response rate in the acute, fulminant form than in the chronic, active form.[78,79] A recently published short- and long-term follow-up study, including 27 paediatric patients with ulcerative colitis, showed that infliximab is more effective in acutely ill patients with ulcerative colitis than in patients with chronic corticosteroid-dependent ulcerative colitis (treatment success, 75% and 27%, respectively).[80]

Other commonly used therapy for the severe, fulminant form of ulcerative colitis is ciclosporin (cyclosporin).[81] Infliximab seems to be an alternative to ciclosporin in the moderate to severe form of ulcerative colitis. The previously mentioned Swedish study by Jarnerot et al.[73] showed infliximab was effective rescue therapy in adult patients, with a severe attack of ulcerative colitis not responding to conventional treatment; however, the beneficial effect of infliximab in the fulminant form of ulcerative colitis was questionable.[82] At present, there has been no comparative study between ciclosporin and infliximab therapy in patients with ulcerative colitis.

In conclusion, limited available data indicate that infliximab treatment is associated with short- and long-term clinical improvement in paediatric patients with moderate to severe ulcerative colitis. This treatment may be beneficial as a 'bridge' therapy until other immunomodulatory drugs become active. It may allow patients to discontinue corticosteroid use and improve nutritional status before colectomy. Nevertheless, larger prospective and controlled studies are necessary to confirm these findings.

2.4 Indeterminate Colitis

Even in adult patients, data are scarce on infliximab treatment in indeterminate colitis. In an open retrospective study, reported by Papadakis et al.,[83] 20 adult patients with indeterminate colitis were treated with infliximab. Seventy percent of patients had a complete response to infliximab treatment, 10% showed a partial response and 20% had no response. It should be noted that during the follow-up, ten patients were re-classified as having Crohn's disease and two with ulcerative colitis. In another retrospective, multicentre study the response rate to infliximab in 11 adult patients with active indeterminate colitis was only 50% at day 7 and 30% after 1 month.[84] There are no paediatric trials in children with indeterminate colitis treated with infliximab.

2.5 Paediatric Extra-Intestinal Manifestations of Inflammatory Bowel Disease

Extra-intestinal manifestations can occur in up to 40% of all patients with IBD, including skin lesions, eye diseases, arthritis, sclerosing cholangitis and others. Infliximab seems to be effective in all systemic manifestations but controlled studies are lacking.

Regueiro et al.[85] reported on successful infliximab treatment of medically refractory pyoderma gangrenosum in 13 adult patients with IBD. Three patients had a complete response to induction infliximab therapy and did not require repeated infliximab administration. Ten patients responded to induction therapy and maintained pyoderma gangrenosum healing with infusions every 4–12 weeks. The only placebo-controlled trial of infliximab therapy for pyoderma gangrenosum in adults exhibited significant efficacy in 46% of patients (6/13) compared with 6% of placebo-treated patients (1/17).[86] Infliximab was effective in children with pyoderma gangrenosum[87] and in the management of peristomal pyoderma gangrenosum.[88]

Eye abnormalities associated with IBD include scleritis, episcleritis and uveitis. Uveitis in patients with IBD is mostly bilateral, posterior, insidious in onset and chronic in duration. On the other hand, uveitis associated with spondyloarthropathy is predominantly unilateral, anterior, sudden in onset and shorter in duration. Infliximab was effective in both types of uveitis in adults[89] and in children.[90]

Beneficial effects of infliximab treatment for childhood uveitis and arthritis are well known,[91,92] but its effect in sclerosing cholangitis is questionable. Silbermintz et al.[93] reported a 13-year-old girl with Crohn's disease, pancreatitis and sclerosing cholangitis treated successfully with infliximab. She subsequently developed granulomatous lung disease. After introduction of infliximab therapy, pulmonary symptoms resolved, and gastrointestinal, pancreatic and hepatobiliary symptoms improved.

The joint disorders associated with IBD include peripheral arthropathy and sacroiliitis or ankylosing spondylitis. Peripheral arthropathy parallels disease activity, and axial manifestations, which have a rather independent course, responded well to infliximab.[94,95]

A patient with metastatic Crohn's disease in the skin of his penis and scrotum, published as a case report previously,[96] improved after receiving repeated infliximab infusions for a year followed by surgery. However, an 11-year-old boy with metastatic Crohn's disease (soft swelling of the penis and scrotum) failed to respond to repeated treatments of infliximab.[97]

2.6 Where to Go: 'Step-Up or Top-Down'

The current approach to Crohn's disease and ulcerative colitis therapy can be best illustrated by the treatment pyramid, or 'step up' approach, in which mesalazine (5-aminosalicylic acid) compounds, antibacterials and nutritional therapy form the base of the pyramid and are used in the case of mild to moderate diaease. As the illness tends towards a more severe disease, the therapy is escalated or 'stepped-up' to include corticosteroids; in case of corticosteroid-dependent or -resistant disease, immunomodulators such as mercaptopurine and methotrexate are utilised. Finally, the use of infliximab and surgery is reserved for the tip of the pyramid.

However, abstracts presented by Hommes et al.[98] and Löwenberg et al.[99] at Digestive Disease Week in 2005 and 2006, respectively, suggested this pyramid could be reversed. In this placebo-controlled trial, 133 patients with Crohn's disease were

randomised to top-down treatment with three infliximab infusions (week 0, 2 and 6) and azathioprine 2–2.5 mg/kg/day or step-up therapy with topical (budesonide 9 mg/day) or systemic (prednisone 40 mg/day) corticosteroids. Overall, treatment success was seen in 29% of top-down and 5% of step-up patients. Remission without corticosteroid use and without resection was attained in 60% of top-down versus 41% step-up patients at 6 months. At the same time 31% of patients in the step-up group were still receiving corticosteroids (median dose 26 mg/day) compared with none of the top-down patients. Serious adverse events were similar in the two groups (49% of top-down and 41% of step-up patients).

Considering the need for a corticosteroid-sparing treatment regimen early in the disease course to promote linear growth velocity in children and adolescents, these data could be applied in the paediatric IBD treatment algorithm. However, controlled trials in similar settings in paediatric IBD patients are clearly needed and the long-term effects of infliximab treatment should be taken into account.

3. Infliximab Safety

3.1 Immunogenicity

The presence of murine components in monoclonal antibodies is associated with a risk of immunogenicity. Antibodies against infliximab (human antichimeric antibody, HACA) were detected in 61% of patients in a prospective study of 125 infliximab-treated adult patients with Crohn's disease.[100] More recently, in a prospective observational study, 36% of adult IBD patients receiving infliximab developed HACA.[101] In this randomised, placebo-controlled trial, administration of a second infliximab infusion within 8 weeks of the first and concurrent immunosuppressant therapy significantly reduced HACA formation. Moreover, intravenous hydrocortisone premedication significantly reduced HACA levels, but did not eliminate HACA formation or infusion reactions. The presence of these antibodies was associated with an increased risk of infusion reactions and loss of response to treatment. In these patients the cumulative incidence of antinuclear antibodies was 57%.[102] Antinuclear antibodies persisted up to 1 year after the last infusion and only a few patients became seronegative. Two patients developed drug-induced lupus erythematosus. Antinuclear antibodies were associated with the female sex and skin manifestations (papulosquamous or butterfly rash). In adults, infusion reactions occur in 3–6% of infliximab infusions, affecting 6–32% of patients depending on concomitant administration of immunosuppressive agents.[103,104]

The safety and effectiveness of infliximab for paediatric patients with Crohn's disease has been investigated previously, but paediatric studies on immunogenicity of infliximab therapy are scant. In our experience, infliximab was well tolerated for multiple infusions, and acute infusion reactions were seen in 15% of 82 patients or in 5.3% of 432 infusions.[105] This corresponds to data in adults, in whom infusion reactions are seen in 4–13% of infusions and in 17–27% of the study population.[39,106,107]

The prevalence of HACA in children receiving infliximab was determined by Miele et al.[108] to be 35%. As described in adult patients earlier,[100] infusion reactions occurred in a higher proportion of infusions given to HACA-positive patients than HACA-negative patients (14% vs 3.6%, respectively), which correlated with antibody levels. In contrast to the adult experience, the interval between infliximab infusions did not influence the titres of HACA in children with Crohn's disease. In this retrospective review, a trend towards a lower prevalence of HACA in children younger than 14 years was observed, which is supported by a previous report by Kugathasan et al.[109] In this study, where infliximab re-treatment of adults with Crohn's disease was compared with children, patients younger than 17 years seemed to tolerate episodic infliximab re-treatment better. There was a significant difference in the rates of severe systemic reaction observed in adults and children (21% vs 3%, respectively). The authors concluded that episodic infliximab re-treatment, mainly a distant second infusion, is associated with high rates of severe systemic reaction in adults but not in children. Candon et al.[54] have found very similar rate of HACA (35.7%) in children with Crohn's disease after infliximab administration. The presence of HACA

was clearly associated with a loss of clinical efficacy. Severe infusion reactions occurred in two patients showing the highest titres of HACA, precluding further use of infliximab. The type of induction therapy (one vs three infusions) appeared to increase the risk of developing HACA. The prevalence of HACA in patients treated with a single infusion was significantly higher than in those treated with three consecutive infusions (78% vs 16%), as also concluded from prospective adult studies.[110-112] Nevertheless, because of the small size of this paediatric study and the large number of patients crossing over, a potential relationship between the schedule of retreatment and HACA development cannot be established.

In the largest paediatric survey to date, a total of 1652 infliximab infusions were administered to 243 paediatric patients.[113] Overall, 60 infusion reactions occurred in 40 patients (16.5% of patients, 3.6% of infusions). Premedication and its role in preventing infusion reactions was also evaluated. No benefit for use of antihistamines, antipyretics or corticosteroids in order to prevent the development of infusion reactions was found. However, once an infusion reaction occurred, premedication was indicated to prevent further infusion reactions.

Infusion reactions occurred in 8.1% of patients (seven early and two delayed) and in 1.2% of all infusions in a retrospective review from Kansas City, in which 594 infusions were administered to 111 IBD patients (including 23 children with ulcerative colitis).[114] Interestingly, reactions occurred more frequently in female than male patients (14% vs 2%, respectively). Gender has also been identified as a risk factor in adults[115] and in children,[114] without a clear explanation for this association. The highest rates of infliximab infusion reactions in paediatric patients with Crohn's disease were published in the previously mentioned study.[114] Thirty-one (8.6%) immediate infusion reactions and four delayed reactions were identified in 57 treated children in a total number of 361 infliximab administrations.

In a prospective study in 21 children with Crohn's disease treated with infliximab, antinuclear antibodies were present in 29% of patients, with antibodies to double-stranded DNA in 10%. In contrast to adult studies, these antibodies disappeared within 6 months after discontinuing infliximab.[45] In this study, one patient had acute infusion reaction, namely anaphylactic shock during the second infusion of infliximab. The patient was treated with methylprednisolone, and no further adverse reaction occurred after increasing the infusion time from 2 to 4 hours and pretreatment with the antihistamine dexchlorpheniramine.

A retrospective study from the Netherlands, describing experience with infliximab in 30 paediatric patients (total of 212 infusions) with severe Crohn's disease, reported six patients (20%) with acute allergic reactions during infliximab infusions.[49] Corticosteroids and antihistamines were given intravenously to resolve acute reactions. These drugs were administered as prophylaxis before subsequent infusions. One out of six patients had a severe allergic reaction with dyspnoea, facial oedema and hypoxaemia after the fourth infliximab infusion. It is of interest that 9 years elapsed between her second and third infusion. This was the first paediatric report where severe systemic reactions occurred after an infliximab-free period. The patient received no more infliximab therapy. Moreover, seven patients (23%) experienced other adverse effects such as headache, muscle ache and nausea, and one patient had arthritis of the hip joint after the second infliximab infusion. One patient died of sepsis and is discussed in section 3.2. None of the patients experienced autoimmune phenomena.

Infusion reactions were noted in 13 children (15%), with a total of 16 reactions from 450 infusions (4%) in a multicentre study where 88 children with refractory Crohn's disease were treated with repeated administration of infliximab.[52] Of the 13 patients, ten had further infusions, but a second reaction occurred in only three patients. Adverse reactions during infusion of infliximab consisted of hypotension, headache, fatigue, pruritus, chest tightness, fever, flushing, nausea and tachycardia. Only three patients developed a delayed hypersensitivity reaction: two patients had polyarthralgia and fever 10–14 days after the second or/and the third infusions. One patient developed skin lesions suggestive of lupus erythematosus with no other symptoms and negative antinuclear antibodies. Previous studies have shown that clinical symptoms of lupus er-

Table V. Frequency of acute and delayed infusion reactions, and different type of antibodies in infliximab-treated children with Crohn's disease

Study	Patients (all infusions)	Infusion reactions/ patients (%)	Infusion reactions/ all infusions (%)	Delayed hypersensitivity reactions/ patients (%)	HACA (%)	ANA (%)	Anti-dsDNA (%)
Miele et al.[108]	34 (234)	8/34 (23.5)	18/234 (7.4)	0/34	12/34 (35.3)	ND	ND
Candon et al.[54]	28 (205)	2/28 (7)	2/205 (1)	0/28	10/28 (35.7)	ND	ND
Jacobstein et al.[113]	243 (1652)	40/243 (16.5)	60/1652 (3.6)	ND	ND	ND	ND
Friesen et al.[114]	111 (594)	7/111 (6)	7/594 (1.2)	2/111 (1.8)	ND	ND	ND
Stephens et al.[105]	82 (432)	12/82 (15)	23/432 (5.3)	0/82	ND	ND	ND
Crandall and Mackner[119]	57 (361)	22/57 (39)	31/361 (8.6)	4/57 (7)	ND	ND	ND
Kugathasan et al.[109]	34 (120)	1/34 (3)	1/120 (0.8)	0/34	ND	ND	ND
Cezard et al.[45]	21 (82)	1/21 (5)	1/82 (1.2)	0/21	ND	6/21 (29)	2/21 (9.5)
Lamireau et al.[52]	88 (450)	13/88 (15)	16/450 (3.5)	3/88 (3.4)	ND	ND	ND
de Ridder et al.[49]	30 (212)	6/30 (20)	6/212 (2.8)	1/30 (?) (3.3)	ND	ND	ND
Wewer et al.[53]	24 (116)	3/24 (12.5)	3/116 (2.6)	1/24 (4.2)	ND	ND	ND
All	**752/4458**	**115/752 (15.3)**	**168/4458 (3.77)**	**11/519 (2.12)**			

ANA = antinuclear antibodies; **dsDNA** = double-stranded DNA; **HACA** = human antichimeric antibodies; **ND** = not determined.

ythematosus related to infliximab treatment are rare and generally limited to skin eruption.[116,117] One child presented with Henoch-Schönlein purpura within 1 week after the first infusion of infliximab. This phenomenon has been reported in adults. A 24-year-old woman developed Henoch-Schönlein purpura with biopsy-proven leukocytoclastic vasculitis 9 days after her initial dose of infliximab.[118] Three patients (12.5%) with immediate infusion reactions and one patient (4%) with a delayed reaction of a total of 24 patients were reported by Wewer et al.[53] The acute reactions were anaphylactic symptoms and one patient had episodes of serum sickness.

The frequency of acute and delayed infusion reactions, and different types of antibodies in infliximab-treated children with Crohn's disease are displayed in table V. The most common symptoms of immediate infusion reactions described are flushing and shortness of breath, and the most common symptoms of delayed infusion reactions are joint pain and swelling. Reactions usually occurred during or after the second or third infusion.

Puchner et al.[120] reported successful desensitisation and therapeutic infusion of infliximab in an adult (40-year-old female) and a paediatric patient (10-year-old boy) with Crohn's disease who had previously experienced an anaphylactic reaction.[120] Desensitisation was performed in the intensive care unit. The total amount of infliximab (208mg for the paediatric patient, corresponding to 5 mg/kg) was administered in 11 escalating increments, ranging from 2μg to 80mg. The paediatric patient was not receiving concomitant medications, including corticosteroids, at the time of the desensitisation protocol. Infliximab doses were administered intravenously every 15 minutes, with vital signs obtained before and after each infusion. The patient tolerated the intravenous desensitisation of infliximab over a 4-hour period without incident and experienced clinical improvement. The adult patient showed similar successful desensitisation; however, she continued intravenous corticosteroid therapy (hydrocortisone 300 mg/24 hours) at the time of the desensitisation protocol, which was being used to manage her active IBD.

In conclusion, although the current literature supports use of concomitant immunosuppressive therapy to reduce the risk of antibody formation and infliximab infusion reactions, and to prolong the duration of treatment efficacy, the risk of concomitant immunomodulatory therapy in the light of reported cases of hepatosplenic T-cell lymphoma (HSTCL) needs to be taken into consideration. In cases of infusion reaction, most infusions can be completed after adjustment in infusion rate and with medical therapy. Severe reactions may not be an

absolute contraindication to future infliximab therapy either. Premedication does not prevent the development of infusion reactions; however, it is indicated to prevent subsequent infusion reactions.

3.2 Infections

One of the major concerns with infliximab, as with any immunomodulatory drug, is increased susceptibility to infections. TNF-deficient mice are particularly susceptible to infections, in particular, with *Candida* spp.[121] The most common infections associated with infliximab therapy are tuberculosis, histoplasmosis, listeriosis and herpes zoster. The infection rate of adult IBD patients treated with infliximab is 4–8%.[39,122] In a large cohort study from the Mayo Clinic, 20 of 500 consecutive patients (4%) treated with infliximab experienced serious infections: eight patients had pneumonia (two were fatal), two had fatal sepsis, six viral infections, two an abdominal abscess requiring surgery, one arm cellulitis and one histoplasmosis; a total of ten deaths were observed. The authors assumed that in half of these patients (1%) the events leading to death might be related to infliximab treatment.[122]

The infection rate in children with Crohn's disease in published paediatric trials concerning infliximab treatment was 3.9%. The type and cause of infections are similar in children and adults, but tuberculosis seems to be less common in children.

In the previously mentioned multicentre study (450 infusions in 88 children with refractory Crohn's disease), four patients (4.5%) had severe infections after infliximab infusions, three patients developed abscesses (two perineal, one arm) and one child with a central venous line had septicaemia caused by *Staphylococcus aureus*.[52] In the retrospective review from Kansas City (594 infusions in 111 IBD patients), three patients developed cutaneous tinea infections, and shingles occurred in one.[114] In our experience, three children out of 82 (3.7%) developed herpes zoster, and one patient had meningitis caused by *Listeria monocytogenes*, which was published as a case report.[123]

Severe sepsis or abscess formation could also be associated with infliximab treatment in children. The first observation of a child who died during infliximab therapy was reported by de Ridder et al.[49] The patient was malnourished, had undergone multiple surgical procedures and had leukopenia as a consequence of azathioprine therapy. Lethal bacterial sepsis originating from a hidden abscess has been previously published in the adult literature.[122]

Infliximab therapy has been associated with rare cases of optic neuritis, seizures and multiple sclerosis,[124] and may worsen congestive heart failure in adults.[125] In the paediatric field, a dramatic flare-up was observed in an 11-year old boy with Crohn's disease of an intramyocardial inflammatory process and abscess with positive blood culture (*S. aureus*) after treatment with infliximab.[126] Three days after the first dose of infliximab the patient showed signs of cardiac failure with fever, nausea and myalgia. Echocardiography demonstrated destruction of the aortic valve, with third-grade insufficiency. Despite antimicrobial therapy and rapid improvement, the aortic valve had to be replaced by a homograft because of massive cardiovascular insufficiency.

It is important to emphasise that infliximab is an extremely potent immunomodulator and therefore may influence the protective immune system against infectious agents. The current recommendations for administration of infliximab are to avoid its use in patients with acute infections. Moreover, patients with abscesses or infected intra-abdominal masses should have surgical drainage before treatment with infliximab.

Reactivation of latent tuberculosis is a severe complication of infliximab treatment.[127-129] By February 2005, 709 cases of tuberculosis (62 deaths) in association with infliximab treatment had been reported. The median time from the first infusion to the onset of symptoms was 123 days.[130] Thus, testing for tuberculosis prior to therapy is recommended. However, a high incidence of anergy after administration of intradermal purified protein derivative in IBD patients limits the usefulness of tuberculin skin tests before infliximab therapy.[131] Therefore, evaluation for tuberculosis should include not only a tuberculin skin test, but also a detailed history of travel, tuberculosis exposures, and such symptoms as chronic cough and weight loss, and a chest radiograph should be considered.

3.3 Malignancy

TNF plays an important role in tumour growth control and, therefore, anti-TNF therapy may increase the risk of malignancies. Different trials yielded conflicting results. Data from the TREAT (Crohn's Therapy, Resource, Evaluation and Assessment Tool) registry, which includes 6290 patients with Crohn's disease, showed that the mortality rates were similar for infliximab- and non-infliximab-treated patients.[132] The rate of lymphoma or overall cancer was not higher in patients treated with infliximab than in patients treated conventionally. In contrast, Bongartz et al.[133] found evidence of an increased risk of serious infections and increased risk of malignancies in patients with rheumatoid arthritis treated with infliximab. However, it should be noted that in rheumatoid arthritis the background incidence of lymphoma is increased compared with the general population, and lymphomas have also occurred in patients treated with concomitant immunosuppressive drugs that have malignant potential.[134]

In a multicentre matched pair study, 404 Crohn's disease patients treated with infliximab were matched with 404 Crohn's disease patients who had never received infliximab.[135] Among the 404 patients treated with infliximab, tumour was diagnosed in nine patients (2.2%); of the 404 control patients, seven patients developed neoplasia (1.7%) (OR 1.33; 95% CI 0.46, 3.84; p = 0.40). The survival curve adjusted for patient-year of follow up showed no differences between the two groups studied.

Siegel et al.[136] constructed a decision analytic model to compare the risks and benefits of infliximab treatment with the standard therapy. Results of the simulated model showed that in 100 000 patients at 1 year, infliximab led to 12 216 more patients in remission, 4255 fewer surgical procedures and 33 fewer deaths from flares of disease. However, in this group more lymphomas (201) and more deaths (249) related to complications from infliximab were detected. Interestingly, the infliximab strategy resulted in more quality-adjusted life-years (QALYs) than the standard therapy strategy. The authors concluded that despite an increased risk of lymphoma and death associated with infliximab treatment, the substantial clinical improvement and fewer surgical procedures resulted in an increase in QALYs.

Indirect observations between infliximab treatment and childhood malignancies were assumed in a prospective infliximab trial in 21 children with resistant Crohn's disease. Reactivation of Epstein-Barr virus (EBV) infection in 28% of patients was detected, demonstrated by 100- to 1000-fold increases in their EBV polymerase chain reaction (PCR), which returned to normal after infliximab was discontinued.[45] This observation suggested that retreatment with infliximab may lead to an increased risk of developing EBV-induced lymphoma.

Recently, a fatal case of HSTCL has been described in a 17-year old patient with Crohn's disease treated with mercaptopurine and infliximab.[137] Including this case, nine postmarketing reports of HSTCL have been reported to the FDA as of October 2006.[138] HSTCLs are rare cancers, with about 200 published cases worldwide, and comprise 5% of peripheral T-cell lymphomas. A majority of HSTCL express gamma/delta T-cell receptor gene arrangement. Of the nine cases, eight reported hepatosplenomegaly. All eight patients received infliximab and concomitant immunomodulatory medications (azathioprine or mercaptopurine). In addition, four cases of HSTCL in IBD patients (three azathioprine recipients, one mercaptopurine recipient) were published before infliximab availability, and there are no published HSTCL cases using infliximab alone or in combination with methotrexate. To collect prospective data concerning infliximab administration and HSTCL, the manufacturer of infliximab is sponsoring a prospective, long-term (20 years) observational registry (The North American Pediatric Inflammatory Bowel Disease Collaborative Registry) of paediatric patients with IBD.[138] The Registry intends to collect information on all serious adverse events associated with infliximab administration. A boxed warning for HSTCL was added to the revised product labelling in the US in August 2006.

Taken together, these nine cases, with an almost uniform fatal outcome, raise an important question for the paediatric population facing possible long-term maintenance infliximab therapy and concomitant anti-metabolite therapy.

4. Home Infusion Programme

In carefully selected paediatric patients with IBD, infliximab infusions administered at home were safely administered and cost-effective. Ten children with IBD in remission (nine patients with Crohn's disease and one with indeterminate colitis) were enrolled in this home infusion programme if they had previous hospital-based infliximab infusions (at least three times) with no adverse events, and had access to experienced paediatric homecare nursing. A total of 59 infusions were administered. The calculated average savings per patient was $US1335 per 100mg of infliximab. Since infusions could be given any day of the week, absence from school was decreased. This programme was associated not only with significant cost saving, but excellent patient and family satisfaction. The average patient satisfaction rate was 9 on a scale from 1 to 10 (10, most satisfied). No severe adverse events occurred during home infusions and only one infusion was discontinued, because of arm pain above the intravenous site.[139]

5. Conclusions

Infliximab is frequently used in paediatric patients with IBD. The medication is administered at various points in the course of the disease: (i) at the point when Crohn's disease is determined to be refractory to other therapy; (ii) possibly early on in severe perianal Crohn's disease; (iii) in ulcerative colitis unresponsive to conventional therapy; and (iv) in severe, acute ulcerative colitis exacerbations unresponsive to a course of intravenous corticosteroids. The current clinical practice is to administer infusions at 0, 2 and 6 weeks, followed by maintenance infusions every 8 weeks. Studies suggest that the timing of delivery of this medication, in relation to the duration of disease, is not related to improved results, and that the maintenance therapy prolongs its effect. The most common adverse event (infusion reaction) may not preclude further use of this therapy. Schedules that include infusions at every 8-weeks appears to be preferable over the longer term. Careful attention should be paid to the potential adverse events, especially infections and malignancy.

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