

Infliximab Dependency in Pediatric Crohn's Disease: Long-term Follow-up of an Unselected Cohort

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Background: Infliximab is effective for induction and maintenance of remission in Crohn's disease. It is unknown how long patients should be kept on infliximab therapy. The primary aim of this study was to assess duration of effective maintenance therapy and infliximab dependency in pediatric CD patients initially responding to infliximab therapy.

Methods: All pediatric patients treated with infliximab by pediatric gastroenterologists in the Netherlands because of severe luminal or fistulizing CD with initial response to infliximab therapy were reviewed. Duration of therapy, clinical response and adverse events were recorded.

Results: Sixty-six CD patients (37 boys) in 10 hospitals were initially responding to infliximab therapy. Mean age at the start of infliximab therapy was 14.5 years (range, 8.1-18.5 years). Mean follow-up since infliximab was started was 41.3 months (range 12-165). In total, 991 infusions were administered. Analysis demonstrates that 15.2% of patients had prolonged response, while 56.1% were infliximab dependent and 28.8% lost response. In total, 10 patients (15.2%) developed an infection during infliximab therapy and 8 (12.1%) had an immediate allergic reaction.

Conclusions: Good clinical response to maintenance infliximab therapy was seen in 70% of patients. Infliximab maintenance therapy seems very effective and safe in pediatric CD. However, more than half of the patients in this cohort is dependent on

repeated infliximab infusions. The number of infliximab infusions received when patients lost response to infliximab was diverse. There was no statistical difference regarding response to infliximab therapy when started early as compared to later in the course of Crohn's disease.

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Key Words: pediatrics, biologic therapies, adverse events

Infliximab (Remicade) is a chimeric monoclonal antibody (75% human, 25% murine) that binds human tumor necrosis factor- α (TNF- α), a cytokine with a central role in the pathogenesis of many T-cell-mediated inflammatory processes.^{1,2} In adult patients with active Crohn's disease (CD), large randomized controlled trials have shown the efficacy and safety of infliximab for the induction and maintenance of remission.³⁻⁶ Recently, a large multicenter open-label randomized controlled trial in children and adolescents demonstrated that infliximab is a very potent drug in a population that is not responding to standard therapies.⁷ To date, however, no data on children are available with respect to the duration of effective infliximab maintenance therapy. With respect to efficacy, it has been suggested that the use of infliximab is more effective early in the disease process instead of waiting until conventional therapy has failed. The early stages of immune-mediated disease may be more susceptible to immunomodulation and the natural history of CD may be altered.^{8,9} In children prolonged duration of response after infliximab therapy is reported when the drug was initiated early in the disease course.^{10,11} As yet, it is unknown how long patients should be kept on infliximab infusions once starting therapy and when during the course of the disease patients should start with infliximab. Therefore, the aim of this study was to describe long-term follow-up on pediatric CD patients with luminal or fistulizing disease initially responding to infliximab therapy, and to address the issue of duration of maintenance therapy and infliximab dependency. The second aim was to evaluate the efficacy of infliximab in CD in relation to disease duration in children.

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TABLE 1. Definitions of Response to Infliximab Infusions in Pediatric-onset CD

Initial response	Good clinical response after infliximab induction therapy (0, 2, 6 weeks)
Prolonged response	Maintenance of good clinical response minimally 90 days after last infliximab infusion
Infliximab dependency	Relapse of symptoms requiring repeated infliximab infusions regaining good clinical response
Lost response	Initially good clinical response but finally withdrawal of infliximab and switch of medical therapy or need for surgery
Good clinical response	Judgment of treating physician
Good response fistulas	Closure or cessation of drainage maintained for >4 weeks

MATERIALS AND METHODS

We reviewed all pediatric CD patients treated by pediatric gastroenterologists with infliximab in the Netherlands. In 2002, a study group of the Dutch pediatric gastroenterological society composed a consensus guideline for infliximab treatment of children with severe CD. Since then, all pediatric gastroenterology units in the Netherlands were visited yearly to collect data on infliximab-treated children and adolescents with CD.¹² Patients were included in this study in case infliximab was started before the age of 19 years because of severe luminal or fistulizing CD and if they showed an initial response (defined in Table 1) to infliximab therapy. Patients in whom infliximab was withdrawn after 1–3 infusions in total and were switched to other medical therapy or needed surgery were considered initial nonresponders to infliximab and were therefore excluded from this study. Data on patient characteristics, disease history, previous treatment, adverse events, number and schedule of infliximab infusions, and surgery were extracted from the medical records. Data collection was closed on the first of June 2007. The outcome of infliximab therapy was defined as prolonged response, infliximab dependency, or lost response. These definitions are further clarified in Table 1. Statistical analysis was performed using SPSS (Chicago, IL). Prolonged response was compared to no prolonged response in fistulizing and nonfistulizing patients using Fisher's exact tests. The long-term response to infliximab was analyzed in patients starting infliximab within or after 1 and 2 years since diagnosis using Fisher's exact tests. A *P* value <0.05 was considered significant.

RESULTS

Between October 1, 1992, and June 1, 2007, 66 CD patients (37 boys) were treated with infliximab in 10 hospitals

TABLE 2. Patient Characteristics at the Beginning of Infliximab Therapy (*n* = 66)

	<i>n</i>	%
Gender		
<i>Male</i>	37	56.1
<i>Female</i>	29	43.9
Age at diagnosis, mean (range) in years	12.2 (2.7–16.7)	
Localization		
<i>Ileal</i>	5	7.6
<i>Colonic</i>	30	45.5
<i>Ileo-colonic</i>	31	47.0
Fistulas		
<i>Perianal</i>	19	30.6
<i>Rectovaginal</i>	1	1.6
<i>Recto-urethral</i>	1	1.6
Operated patients	13	21.0
Previous treatment		
<i>5-Amino-salicylic acids</i>	45	68.2
<i>Corticosteroids</i>	63	95.5
<i>Azathioprine</i>	57	86.4
<i>Methotrexate</i>	16	24.2
<i>Antibiotics</i>	17	25.8
<i>Exclusive enteral nutrition</i>	10	15.2
Indication for infliximab		
<i>Refractory luminal CD</i>	39	59.1
<i>Refractory luminal CD plus growth retardation</i>	8	12.1
<i>First line luminal CD</i>	1	1.5
<i>Fistulas</i>	10	15.2
<i>Refractory luminal CD plus fistulas</i>	8	12.1

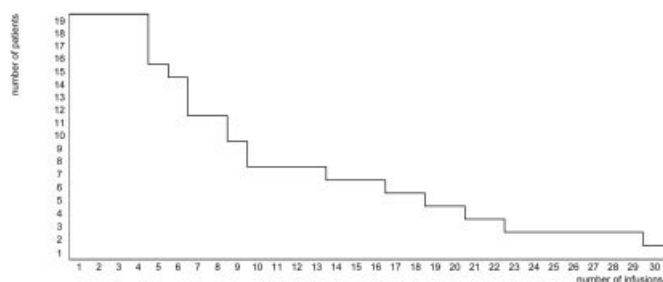
(7 academic and 3 nonacademic centers) (Table 2). Two patients were excluded from this study because of initial nonresponse to infliximab. Mean age at diagnosis was 12.2 years (range, 2.7–16.7 years). Patients were refractory to conventional treatment consisting of either solitary enteral nutrition, 5-aminosalicylic acid, or high-dose corticosteroids for a minimum of 3 weeks as remission induction. As maintenance therapy they were treated with either adequately dosed azathioprine (2.5–3.0 mg/kg) or methotrexate (15 mg/m²) for a minimum of 4 months (unless adverse events to these drugs prohibited further usage). One patient was an exception and was not refractory to conventional treatment. This patient presented with such severe clinical and endoscopic colonic CD that first-line infliximab therapy was administered.¹³ The majority of patients received a 3-dose induction scheme at 0, 2, and 6 weeks followed by maintenance therapy as judged by the clinician every 8 weeks. The dosage of infliximab was 5 mg/kg. Five out of 66 patients received infliximab episodically instead of maintenance. Two out of

TABLE 3. Infliximab Infusions in Pediatric-onset CD Patients ($n = 66$) and Outcome

Mean age at start of infliximab therapy in years (range)	14.5 (8.1–18.5)
Mean time between diagnosis of CD and start of infliximab therapy in years (range)	2.4 (0–7.5)
Total number of infusions, mean (range)	991, 15.0 (3–64)
Concomitant medication (%)	
Corticosteroids	8 (12.1)
Thiopurine	42 (63.6)
Methotrexate	15 (22.7)
Antibiotics	3 (4.5)
Outcome (%)	
Prolonged response	10 (15.2)
Infliximab dependency	37 (56.1)
Lost response	19 (28.8)
Mean duration of infliximab therapy in months (range)	28.9 (2–108)
Mean follow-up since start of infliximab therapy in months (range)	41.3 (12–165)
Surgery since start of infliximab therapy (%)	26 (39.4)
Bowel resection	23 (34.8)
Fistula correction	6 (9.1)

the 5 patients had prolonged response, while the other 3 patients had lost response.

It was not routinely attempted to stop infliximab. However, 21 out of 37 (57%) patients in whom infliximab infusions were continued either developed symptoms again at the end of the infliximab interval, necessitating shortened intervals or dosage increase up to 10 mg/kg. Mean age at the start of infliximab therapy was 14.5 years (range, 8.1–18.5 years) (Table 3). Mean follow-up since the start of infliximab was 41 months (range, 12–165 months). In total, 991 infliximab infusions were administered, 3–64 per patient (mean, 15.0). Analysis of the entire cohort demonstrates that 15.2% of patients had prolonged response, while 56.1% were infliximab-dependent and 28.8% lost response (Table 3). The patients who had prolonged response received between 3 and

**FIGURE 1.** Patients with lost response to infliximab therapy related to total amount of infliximab infusions received.**TABLE 4A.** Statistical Significance of Response to Infliximab Related to Starting Infliximab Within or After 1 Year (Fisher's Exact Test)

	≤ 1 year; $n = 16$	> 1 year; $n = 50$
Prolonged response/dependency (%)	10 (62.5)	37 (74.0)
Lost response (%)	6 (37.5)	13 (26)
$P = 0.53$.		

8 (mean, 6) infliximab infusions in total. The patients who eventually lost response received between 4 and 30 (mean, 12) infliximab infusions in total (Fig. 1).

Fifteen patients (22.7%) stepped up to 10 mg/kg infliximab because of decrease in response and in 25 patients (37.9%) the interval was shortened to 4–7 weeks because of loss of effect before the end of the 8-week interval. Twenty-six patients (39.4%) needed surgery despite the use of infliximab (Table 3). Six of them, all dependent on infliximab infusions, underwent surgery because of stenosis ($n = 1$), abscess ($n = 2$) and intercurrent exacerbation ($n = 3$). One patient initially had prolonged response on infliximab but experienced an exacerbation 6 months after discontinuation of infliximab treatment and underwent partial ileal resection.

There was no statistical difference regarding response to infliximab therapy when started within 1 or within 2 years after CD was diagnosed as compared to later than 1 or 2 years after diagnosis (Table 4a/b). A total of 48 patients had luminal CD without fistulas. Two of them (4.2%) had a prolonged response, while 30 patients (62.5%) were dependent on infliximab infusions (Table 4c). In the group of 18 patients with fistulizing CD, however, 9 (50.0%) had prolonged response and 7 (38.9%) were dependent on infliximab infusions to maintain response. Thus, prolonged response occurred significantly more often in patients with fistulizing disease compared to those CD children without fistulas.

Adverse Events

In total, 10 patients (15.2%) developed a (mostly mild) infection during infliximab therapy (Table 5). A 14-year-old

TABLE 4B. Statistical Significance of Response to Infliximab Related to Starting Infliximab Within or After 2 years (Fisher's Exact Test)

	≤ 2 years; $n = 36$	> 2 years; $n = 30$
Prolonged response/dependency (%)	24 (66.7)	23 (76.7)
Lost response (%)	12 (33.3)	7 (23.3)
$P = 0.42$.		

TABLE 4C. Statistical Significance of Response to Infliximab Related to Fistulizing or Nonfistulizing Disease (Fisher's Exact Test)

	Nonfistulizing; <i>n</i> = 48	Fistulizing; <i>n</i> = 18
Prolonged response (%)	2 (4.2)	9 (50.0)
Infliximab dependency/ lost response (%)	46 (95.8)	9 (50.0)
<i>P</i> < 0.05.		

boy developed multiple stenoses of the ileum after the third infliximab infusion and had to be operated on. Serum sickness-like disease, drug-induced lupus, cancer, demyelination, or heart failure were not seen in this patient cohort.

Infusion Reactions

Eight out of the 66 patients (12.1%) had an immediate allergic reaction during infusion (Table 5). One of them received corticosteroids as the only concomitant medication, all others received azathioprine for 3 months or more. In all but 1, reactions resolved after administration of intravenous corticosteroids and an antihistamine. One patient needed intravenous administration of epinephrine. The allergic reaction in this patient was preceded by an infliximab-free interval of 9 years; no prophylaxis (such as corticosteroids and antihistamine) was given before restarting infliximab.¹² Infliximab therapy was discontinued. In 2 more patients infliximab treatment was also discontinued because of allergic reactions. One was a 15-year-old boy, who had an infliximab-free interval of 13 months between the third and fourth infusion who developed an allergic reaction on the fourth infusion. Despite prophylaxis, allergic reactions reoccurred during further treatment. The other, a 17-year-old girl, had an allergic reaction with her 20th infliximab infusion, 26 months after the

TABLE 5. Adverse Events in Pediatric CD Patients (*n* = 66) Treated with Infliximab

Infections	10
<i>Gastroenteritis</i>	3
<i>Tinea capitis</i>	2
<i>Verrucae plantares</i>	2
<i>Chickenpox</i>	1
<i>Pneumonia</i>	1
<i>EBV</i>	1
Acute infusion reactions	8
Stenosis	1
Coxitis	1
EBV, Epstein-Barr virus.	

first one. Intravenous corticosteroids and antihistamine were given as prophylaxis before subsequent infusions. At the same time, however, she lost response, which was not reversed after stepping up to 10 mg/kg infliximab. Antibodies to infliximab were not routinely checked in these patients.

DISCUSSION

This study describes the longest follow-up of a large pediatric CD cohort receiving repeated infusions of infliximab. The cohort is unselected and therefore mirrors daily practice. In our study, good clinical response to maintenance infliximab therapy was seen in more than 70% of patients, with a mean follow-up of 41 months. However, almost 60% of this cohort appears dependent on repeated infliximab infusions. If patients lost response to infliximab, this was seen after a diverse number of infliximab infusions.

Prolonged response was significantly more often seen in fistulizing CD. Since these patients did not undergo surgical fistula correction at the same time, this seems to indicate that in these cases response to infliximab is truly better.

Infliximab was not routinely stopped; therefore, some patients may be classified as dependent while they might have had prolonged response in case infliximab was stopped. However, in patients where infliximab was not stopped, treating physicians decided not to do this since patients developed symptoms again at the end of the infliximab interval and they considered the risk of flaring was high. This is illustrated by the finding that 21 out of the 37 (57%) patients with infliximab dependency necessitated shortened intervals and/or dosage increase up to 10 mg/kg.

Recently, a randomized, multicenter, open-label study (REACH) was conducted in pediatric CD patients (*n* = 112) to evaluate the short-term safety and efficacy of infliximab maintenance treatment. Responding patients were randomized at week 10 to receive infliximab every 8 weeks (*n* = 52) or every 12 weeks (*n* = 51) through week 46. Response to infliximab was almost 90% at week 10. At 54 weeks, 64% of patients (33 of 52) receiving infliximab maintenance every 8 weeks had a clinical response as assessed by the pediatric Crohn's disease activity index (CDAI) (decrease from baseline ≥ 15 and ≤ 30 total), compared with 33% (17 of 51) in the every-12-week maintenance group (*P* < 0.001).⁷ These data suggest that the effect of infliximab treatment in children may be more favorable than that in adult patients, both regarding remission induction and maintenance therapy. Explanations may be a higher percentage of concomitant immunomodulation, less smoking, and the shorter mean duration in a pediatric compared to an adult CD population.

Wewer et al¹⁴ demonstrated that out of a total of 24 pediatric CD patients, 29% were unresponsive to infliximab, 29% had a prolonged response after discontinuation of infliximab therapy, and 42% were dependent on infliximab rein-

fusion. Follow-up was 90 days after intended cessation of infliximab therapy. These results are quite similar to those of our study cohort.

Since this was a retrospective study and different schedules for patient visits were used, it was not possible to use the pediatric CDAI or another index to score patients at set timepoints. However, we believe that by using the response definitions mentioned above the clinical efficacy of infliximab is sufficiently reflected.

In an open-label, prospective clinical trial Kugathasan et al¹⁰ found that the therapeutic effect of infliximab was sustained longer in pediatric patients with CD treated early in the disease course (disease duration at the start of infliximab treatment less than 2 years) compared to patients with long-standing CD (more than 2 years). In a retrospective study, Lionetti et al¹¹ found that children diagnosed with CD less than 1 year before had higher chances of a longer duration of response than children diagnosed more than 1 year before. In contrast to these findings, we were not able to show a difference in response between early and late disease for more or less than both 1 as well as 2 years interval between diagnosis and start of infliximab (Table 4).

The main adverse events in our patient cohort were infections and infusion reactions. Infections were seen in 15% of our patients, but were usually mild. Pooling of several pediatric studies shows that serious adverse events were described in 4.7% (26 out of 548) of patients, being *Listeria monocytogenes* meningitis ($n = 1$), serious or unusual infections such as abscesses, reactivation of Epstein-Barr virus and shingles ($n = 22$), and intestinal strictures ($n = 3$).^{7,11,14–21}

Allergic reactions during infliximab therapy occurred in 11.3% of our patients, which is quite comparable to the 3 cohort studies determining the rate of infusion reactions, being 8.5%, 8.1%, and 16.5%, respectively, of patients.^{21–23}

The numbers of children with CD treated with infliximab are still too small and follow-up still too short to give proper information about the safety profile. This is illustrated by the postmarketing surveillance data reporting the occurrence of 8 cases of hepatosplenic T-cell lymphoma (6 out of 8 with a fatal outcome) in young CD patients out of $\approx 270,000$ CD patients treated with infliximab.²⁴

In conclusion, infliximab is a very effective therapy in a pediatric population with CD that is not responding to standard therapies. This study shows a good clinical response to infliximab therapy in 70% of patients. In contrast to others, we did not find any statistical difference regarding response to infliximab therapy when started within 1 or within 2 years after CD was diagnosed, as compared to after 1 or after 2 years.^{10,11} It is important to note, however, that almost 60% of this cohort is apparently dependent on repeated infliximab infusions. In patients with fistulizing disease, prolonged response to infliximab therapy was seen in 50%. Based on these

findings and other pediatric and adult studies performed hitherto, the best therapeutic strategy for pediatric patients with refractory luminal CD seems to be maintenance infliximab therapy. However, thorough evaluation of the efficacy and safety of infliximab and of the optimal therapeutic strategy in children is still mandatory. This will require the development of infrastructure and financial support to perform proper multicenter pediatric trials.

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