

Infliximab Therapy in Pediatric Patients 7 Years of Age and Younger

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ABSTRACT

Background: Infliximab (IFX) is efficacious for induction and maintenance of remission in pediatric patients with moderate-to-severe inflammatory bowel disease (IBD). It has, however, not been studied in patients 7 years old and younger. Our aim was to characterize efficacy and safety of IFX therapy in this cohort.

Methods: This was a retrospective study of patients with IBD ages 7 years and younger, treated with IFX between 1999 and 2011. Medical records were reviewed for age of diagnosis, disease phenotype, therapy, surgery, IFX infusion dates, dose, and intervals. Outcome measures included physician global assessment, corticosteroid requirement, and adverse events.

Results: Thirty-three children (ages 2.4–7 years) were included. Twenty patients had Crohn disease, 4 had ulcerative colitis, and 9 had indeterminate colitis. Maintenance of IFX therapy at 1, 2, and 3 years was 36%, 18%, and 12%, respectively. Patients of age 5 years and younger had the lowest rates of maintenance of therapy at 25% at year 1, and 10% at years 2 and 3 combined. Nine percent of all of the patients demonstrated response measured by the physician global assessment and were steroid free at 1 year. There were 8 infusion reactions. There were no malignancies, serious infections, or deaths.

Conclusions: IFX demonstrated a modest response rate and a low steroid-sparing effect in patients with IBD 7 years old and younger. Although this is a limited study, there appears to be a trend for decreased sustained efficacy with IFX in this age group, particularly in children 5 years old and younger, when compared with the previously published literature in older children.

Key Words: infliximab, maintenance of therapy, response rate

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Inflammatory bowel disease (IBD) is a chronic inflammatory disease of the gastrointestinal tract comprising Crohn disease (CD), ulcerative colitis (UC), and indeterminate colitis. The interaction among host genomics, dysregulated immune response, and

environmental factors, principally the gut microbiota, plays a critical role in the pathogenesis of IBD. Tumor necrosis factor (TNF)- α has been shown to be an important cytokine in the development of inflammation in IBD (1). Anti-TNF therapies have been shown to be effective in the treatment of both CD and UC, through binding and neutralizing with high affinity to both soluble and transmembrane forms of TNF- α and by blocking the ability of TNF to bind to its receptor (2,3–5). Maintenance therapy with infliximab (IFX) in adults has resulted in a significant decline in the use of corticosteroids (3,4,6,7). Infliximab was first used in pediatrics in 1998, yet was not approved for use in pediatric CD until 2006.

The REACH (Randomized, multicenter, open-label study to Evaluate the safety and efficacy of Anti-TNF Chimeric monoclonal antibody in pediatric subjects with moderate to severe Crohn's disease) study, a randomized multicenter, open-label trial, evaluated the safety and efficacy of IFX in pediatric subjects age 8 years and older with moderate-to-severe CD on maintenance therapy with immunomodulators (8). This study included 112 patients and demonstrated an overall response rate of 88% and remission in 59% of patients following induction treatment. During the follow-up, the authors described the long-term use of IFX in this cohort and demonstrated significant rates of sustained response and remission in patients who continued receiving IFX maintenance infusions (9). There are no data, however, evaluating the use of IFX in patients 7 years old and younger, which is a particularly difficult population to treat (10). This study was performed to evaluate the use of IFX in this young population.

The primary aim of this study was to evaluate IFX efficacy in patients age 7 years and younger. The secondary aim was to evaluate the safety of IFX in this cohort.

METHODS

This was a retrospective study that included pediatric patients with IBD, ages 7 years or younger, who were treated with IFX at The Children's Hospital of Philadelphia in the years 1999–2011. The inclusion criteria included pediatric patients with a documented history of IBD, including CD, UC, and indeterminate colitis, diagnosis established using standard criteria (endoscopy, radiology, and clinical findings), and who received infliximab by the age of 7 years. Concomitant use of immunomodulators, steroids, or other therapies was not an exclusion criteria. Exclusion criteria included patients whose records were incomplete or who were lost to follow-up.

Medical charts, IBD databases, pharmacological databases, and infusion records were reviewed. Medical charts were reviewed to determine demographic information, disease type, location, severity, surgical history, prior medications, and concomitant medications at induction and throughout IFX therapy. Growth and nutrition were assessed by height and weight z scores. Records were reviewed for

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date of IFX initiation, dose and interval of therapy, and duration of therapy. Episodic versus maintenance therapy was recorded. Induction of therapy was defined as completion of doses at weeks 0, 2, and 6. Escalation of dose was defined if the dose was increased from 5 mg/kg or if the time interval between doses was decreased. Disease exacerbation or remission during treatment was noted throughout therapy. In addition, medical records were searched to determine whether adverse reactions to IFX developed.

Outcome Measures

Primary outcome measure of efficacy was assessed at completion of induction, year 1, 2, and 3, or the final infusion. Sustained clinical response was defined as mild or inactive disease as measured by the physician global assessment (PGA) while receiving IFX without concomitant steroids or surgery. Adverse events were recorded for each infusion.

Statistical Analysis

Categorical variables were summarized by frequencies while continuous variables were summarized by using mean, median, standard deviation, and range. Categorical variables were compared using χ^2 analysis. Continuous variables were compared using the Student *t* test or the Wilcoxon rank-sum test, depending on whether the data were normally distributed. This study was approved by the institutional review board at The Children's Hospital of Philadelphia.

RESULTS

Patient Characteristics

Thirty-three patients were included in the study. The age range was 2.4 to 7.75 years, and 20 patients were age 5 years and younger. Twenty patients had CD, 3 patients had UC, and 10 patients had indeterminate colitis. Indeterminate colitis was defined by the authors as IBD in patients in whom clear criteria were not

present to correctly classify as UC or CD at diagnosis. Twenty-seven (81%) patients underwent an immunological evaluation owing to the early onset of their disease presentation. One patient was found to have immunodysregulation polyendocrinopathy enteropathy X-linked syndrome and 1 patient was found to have an undefined immunodeficiency. Patient demographics and disease classification are described in Table 1.

Efficacy at Year 1

Twelve patients completed 1 year of therapy, of whom 25% (*n* = 3) of patients demonstrated clinical response by PGA, either improving from active or mild disease to inactive disease, or from active to mild disease (*P* = 0.003). Twenty-two subjects (66%) demonstrated response to induction of therapy as measured by the PGA. All of the patients who responded at 12 months demonstrated response at induction. When evaluating by disease type, patients with CD had a 10% (*n* = 2) response rate at 1 year. There was a 25% (*n* = 1) response rate in patients with UC and 0% response in patients with indeterminate colitis.

IFX Dose and Regimen

The total number of infusions was 323, and the duration of therapy ranged from 1 week to 8 years. Induction regimen consisted of interval dosing at weeks 0, 2, and 6. The induction dose was 5 mg/kg, except in the case of 2 subjects who received 10 mg/kg for the initial dosing. Thirty-one (87%) patients completed the induction regimen. Two patients did not complete the induction. One patient discontinued therapy after achieving remission following the second dose and 1 patient with UC required colectomy.

Following induction, 2 patients received episodic dosing of IFX. The remainder of patients received scheduled dosing. The 2 patients who received episodic therapy did not achieve response measured by the PGA and did not continue maintenance therapy at 1 year. Scheduled dosing was at 12-week intervals for 1 patient and for the remainder of patients was 8-week dosing.

Nineteen patients (58%) required dose escalation of IFX or decrease interval of infusions, 2 during induction, and 17 throughout the maintenance phase. Of the 7 patients who continued on maintenance therapy and did not have the dose of IFX increased, 2 developed human anti-chimeric antibodies (HACA) and therapy was discontinued, 1 patient had a reaction, 1 patient was in remission and the family elected to discontinue therapy, and 1 patient had a good response to 5 mg/kg and remains on that dose. There were 2 patients whose initial dosing was 10 mg/kg, and therefore was not included in dose escalation.

Maintenance of Therapy

Of the 33 patients who initiated IFX therapy, 36%, 18%, and 12% of patients continued maintenance therapy at years 1, 2, and 3, respectively (Fig. 1). Figure 2 depicts patient flow. Following induction (which 2 patients did not complete as described above), 7 patients discontinued therapy. Of the 24 patients who began maintenance IFX therapy, 12 patients (57%) patients discontinued before completing 1 year of therapy. Eighty-three percent of patients discontinued therapy for reasons other than for parental requests.

Stratifying by Age

Patients who were age 5 years and younger had the lowest rates of maintenance of therapy overall, 5 patients (25%) continued therapy at 1 year, and 2 patients (10%) continued at years 2 and

TABLE 1. Patient demographics

Age mean (range), y	5.6 (2.4–7.75)
≤5 y, n (%)	20 (59)
6 y, n (%)	5 (16)
7 y, n (%)	8 (25)
Sex, n (%)	
Male	19 (59)
Female	14 (41)
Disease type, n (%)	
CD	20 (61)
Inflammatory	12 (60)
Strictureing	7 (35)
Penetrating and strictureing	1 (5)
UC	3 (12)
Indeterminate colitis	10 (27)
Inflammatory	8 (80)
Penetrating	1 (10)
Strictureing	1 (10)
Disease location (N = 33, all subjects), n (%)	
Colonic only	17 (52)
Ileocolonic	16 (48)
Proximal upper disease	12 (36)
Proximal + distal disease	1 (3)
Perianal disease	2 (6)

CD = Crohn disease; UC = ulcerative colitis.

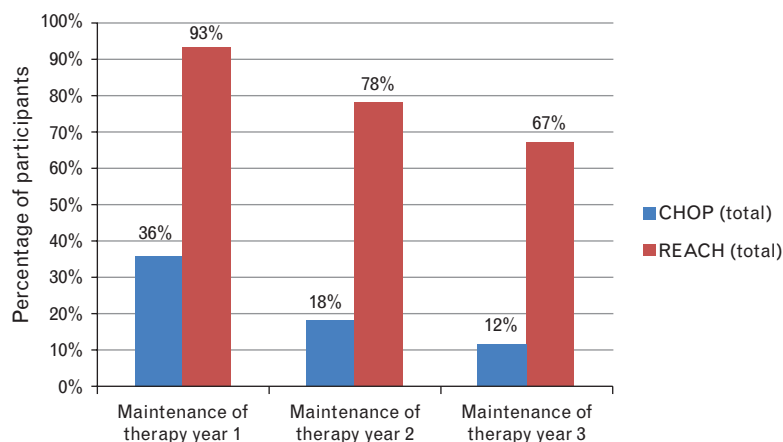


FIGURE 1. Comparison of maintenance of therapy between CHOP and REACH. CHOP = The Children's Hospital of Philadelphia; REACH = Randomized, multicenter, open-label study to Evaluate the safety and efficacy of Anti-TNF Chimeric monoclonal antibody in pediatric subjects with moderate to severe Crohn's disease.

3 combined. This is compared with the 6- and 7-year-olds in this study and with the older cohort depicted in the REACH study. Figure 3 depicts maintenance of therapy stratified by age. In addition, patients 5 and younger had the lowest response rate, 1 patient (5%), as compared with the older cohorts (Fig. 3).

IFX Levels

There were 22 patients who had IFX trough levels obtained throughout therapy. Five patients (15%) were HACA positive. There were 9 patients (27%) who were HACA negative and had no circulating IFX at the time of the infusion at a minimum of 1 point during therapy. Four of these patients had loss of response or no response (44%) and discontinued therapy, 3 patients had an

infusion reaction, and 2 maintained therapy (22%) at 1 year; however, they did not demonstrate response measured by PGA at 1 year and therapy was escalated. Both of these patients eventually underwent a diverting ileostomy. Six of the 9 (67%) patients were on dual therapy. These patients had active disease (as measured by PGA) at the time of evaluation of circulating levels. Eight patients had detectable levels and negative HACA. Five of these patients (63%) continued therapy at 1 year (3 maintained clinical response), 2 had an infusion reaction, and 1 had loss of response. Of the 2 patients who received episodic therapy, 1 developed antibodies.

Concomitant Therapy

At the time of IFX induction, 50% ($n = 17$) of patients were taking antibiotics, 59% ($n = 19$) were taking 5-aminosalicylic acid, and 63% of patients were on immunomodulator therapy (15 on 6-mercaptopurine or azathioprine and 3 on methotrexate). At the end of year 1 of treatment with IFX, 25% of the 12 patients who completed 1 year of therapy 3 remained on dual therapy with immunomodulators. Of these patients 1 achieved response at 1 year. Of those patients on dual therapy at induction, 6 had an infusion reaction (33%).

Twenty-five percent of all patients who completed 1 year of IFX therapy remained steroid free at the end of year 1. This is compared with 53% of patients who were taking corticosteroids at the time of induction of therapy ($P < 0.001$).

Post-IFX

Of those patients who discontinued therapy, 11 patients were initiated on adalimumab, 6 were treated with 6-mercaptopurine or azathioprine, and 5 with methotrexate. There were 6 patients (18.5%) who underwent surgical resection; 83% of these patients did not complete 1 year of therapy. Five of the patients (83%) who went to surgery were 5 years old or younger.

Safety

There were no serious infections or malignancies noted during this study period. In general, the treatment was well tolerated. There were 5 patients who developed antibodies to IFX (HACA); 4 of these patients were age 5 years and younger. There

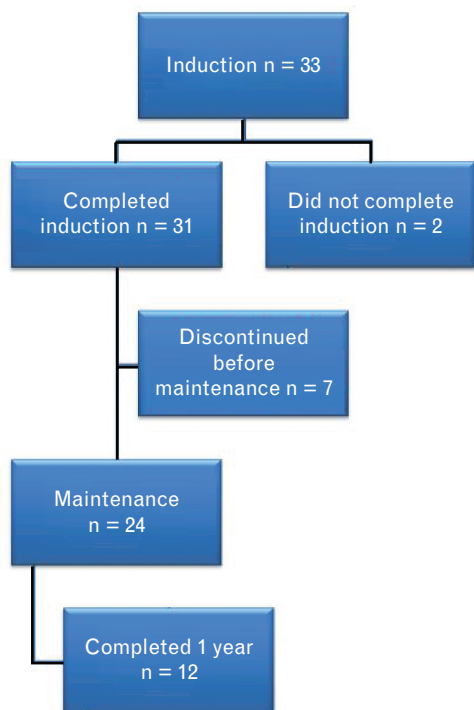


FIGURE 2. Patient flowchart.

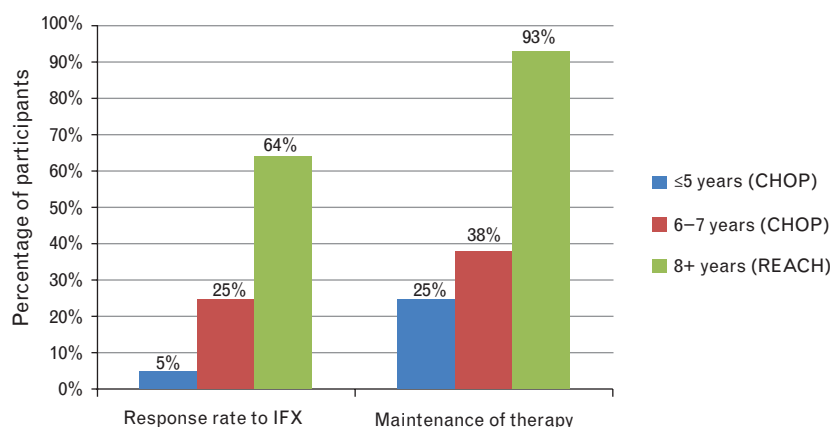


FIGURE 3. Response rate and maintenance of therapy based on age at 1 year. CHOP = The Children's Hospital of Philadelphia; IFX = infliximab; REACH = Randomized, multicenter, open-label study to Evaluate the safety and efficacy of Anti-TNF Chimeric monoclonal antibody in pediatric subjects with moderate to severe Crohn's disease.

were 8 (24%) infusion reactions. Six of these reactions (75%) occurred in patients who were 5 years of age and younger, and 6 patients (75%) were on dual therapy. Five (83%) of these reactions occurred at the second or third infusion.

The infusion reactions included rashes, shortness of breath, and cough during the infusion. The majority of cases resolved with discontinuation of the infusion. Two cases required intravenous (IV) diphenhydramine. One patient developed shortness of breath and oxygen desaturation. This patient required epinephrine, IV diphenhydramine, and IV solumedrol, and the symptoms subsequently resolved. There were 2 patients, one with CD and the other with indeterminate IBD, who developed anaphylactic reactions with the start of the third dose and therapy was discontinued.

Three patients of the cohort received premedication with IV diphenhydramine and IV solumedrol with the initial dose. One patient who received premedication developed a reaction to IFX at 12 months of therapy and was found to be HACA positive. The second patient had no response after 6 months, and while she was HACA negative, she had no circulating IFX at 4-week dosing intervals and therapy was discontinued. The third patient developed an anaphylactic reaction with the second dose of IFX and therapy was discontinued. In addition, steroid premedication was subsequently used for patients who previously reacted to an infusion or were found to be HACA positive (N = 9).

DISCUSSION

There are convincing data that IFX is an effective therapy to induce remission and response in adult and pediatric patients age 8 years and older with CD and UC (4,8,11–13). Together, these studies demonstrated that treatment with IFX can result in improvements in inflammatory markers, such as C-reactive protein and erythrocyte sedimentation rate. The REACH study demonstrated response rates, defined by decrease in the Pediatric Crohn Disease Activity Index (14,15), of 64%, 70%, and 83% at years 1, 2, and 3, respectively. In addition, IFX has also been shown to be beneficial for luminal and fistulizing disease (16,17). To date, however, there are no published data regarding the use of IFX for patients with IBD age 7 years and younger. Because there are significant differences in presentation, location, and severity of disease, we hypothesized that it is possible that these patients respond differently to biological therapy.

The most striking difference compared with previously described experiences with IFX for older children is that children

age 7 years and younger appeared to be less likely to continue IFX maintenance therapy. Of the 33 patients who initiated therapy, 36% completed 1 year of treatment with IFX, 18% completed 2 years of therapy, and 12% completed 3 years of therapy. In comparison, in the REACH cohort of pediatric patients with CD age 8 years and older, 93%, 78%, and 67% continued maintenance therapy at 1, 2, and 3 years, respectively (8) (Fig. 1). Our cohort's rate of maintenance therapy is also lower than a long-term study performed by Crombe et al (18), which evaluated the long-term use of IFX in pediatric patients age 17 years and younger. The investigators studied 120 patients who received IFX between 1999 and 2004. Initial response was 89% at 3 months and 55% retained response at 3 years.

In addition to lower rates of maintenance therapy, there appears to be a decrease in clinical efficacy. At 1 year, patients age 7 years and younger with IBD demonstrated a modest steroid-sparing effect from IFX, 25%, as compared with older children, seen in the REACH study at 64% (Fig. 3). Furthermore, Hyams et al demonstrated that children older than 8 years who continued on maintenance therapy had a response rate of 70% at 2 and 83% at year 3 (9).

When evaluating the response and maintenance of therapy, we noticed an even more striking difference in patients ≤5 years as compared with older children and the REACH cohort. In this study, this group of the youngest children had the lowest rates of maintenance of therapy at year 1 compared with the older children, 6- and 7-year-olds (25% vs 33% and 42%). In addition to this their response rate was only 5% at 1 year (Fig. 3). Furthermore, although unclear why, this cohort appeared to have higher rates of adverse events as well. Six of the 8 (75%) infusion reactions occurred in the extremely young children. It should be noted that there were no serious adverse events. Although the total rate of infusion reactions is similar to REACH (23%) and adult studies (19–21), it is unclear why there was such a strikingly higher proportion of adverse reactions in an extremely young cohort age 5 years and younger. It is possible that pharmacokinetics or the phenotype of predominant colonic disease in the younger population is at least partially responsible for this group's comparatively poor response to IFX. From the data of those patients who began therapy later in the study and had levels obtained (and consistent with the adult literature), patients with circulating IFX and negative HACA were more likely to maintain therapy at 1 year as compared with those without circulating levels (63% vs 44%). A majority of patients (71% of patients in the maintenance phase) in this study required escalation

of therapy. Therefore, this subset of patients may require higher dosing, that is, 10 mg/kg to maintain circulating levels, achieve clinical efficacy, and perhaps prevent the development of antibodies. It is possible that this cohort requires a 10-mg/kg loading dose and a careful monitoring of levels. In addition, it is likely that the disease pathogenesis in this cohort is different from that in older children and adults. It is thought that in at least a subset of these young patients, known as extremely early-onset IBD, the disease involves distinct etiopathogenic pathways, which may reveal an underlying immunodeficiency or single-gene defect (22,23). Those who have been identified thus far have responded to therapeutics directed at the identified pathway. For example, several *IL-10* (24) and *IL-10* receptor (25) gene mutations have been associated with a phenotype of severe perianal disease and colitis in patients with extremely early-onset IBD, particularly in infants. Although only 2 patients in this cohort were subsequently identified to have an immunodeficiency, which may explain the poor response to therapy, it is possible that other patients in this cohort have underlying immunodeficiency or genetic defects that have not yet been identified.

Overall, children age 7 years and younger appeared to have lower response rates to IFX and were less likely to continue the therapy for 1 year or longer. A small proportion of these patients achieved steroid-free remission. In general, IFX was well tolerated in this group, with no serious adverse events; however, there is a potential for increased infusion reactions. Patients age 5 years and younger appeared to experience the least benefit from IFX and had a higher rate of infusion reactions.

There are several limitations to our study, including the relatively small cohort and retrospective design. In addition to this, although REACH only included patients with CD, our cohort was heterogeneous, including patients with UC and indeterminate disease. A further difference that should be noted is that although patients in the REACH study were required to be on dual therapy with an immunomodulator (and have initiated therapy at least 8 weeks before the study), patients in this study were on both monotherapy and dual therapy. The time period of this study may be a factor as well. This study spanned a prolonged time period, in which treatment practices changed owing to concern of malignancy, and the immunomodulator therapy of some of the patients was discontinued during IFX treatment. Because this study took place for a 12-year period, it is important to note that 2 patients received episodic therapy and 1 patient received 12-week dosing, which was common early in the medication's use. These factors may have contributed to the poor response in this cohort, and therefore comparisons need to be interpreted with caution.

Nevertheless, keeping these important limitations in mind, our data suggest the possibility that the youngest patients with IBD have a lesser response to IFX than older children, which may be because of the genomics and immunology unique to the extremely early-onset cohort. A large prospective trial is necessary to answer this question and further evaluate this cohort's response to IFX.

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