

12-Month Follow-up After Successful Infliximab Therapy in Pediatric Crohn Disease

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ABSTRACT

Aim: Infliximab (IFX) therapy is highly efficacious for the induction and maintenance of remission in pediatric Crohn disease (CD). However, to date it is unclear how long patients should be given IFX. Given the increasing safety concerns about the concomitant and prolonged use of IFX and azathioprine in CD, we wanted to address the clinical outcome in pediatric CD patients who responded to IFX medication, once IFX was stopped.

Patients and Methods: Upon induction therapy with 3 IFX infusions, 36 of 38 patients with CD were in clinical remission at 3 months. These 36 responders were separated into 2 groups: 16 patients received no further IFX infusions, whereas 20 patients received scheduled maintenance therapy with IFX for 12 months.

Results: Among the 16 patients who received no further IFX infusions, 12 experienced relapse during the 12-month follow-up interval after IFX was stopped. In the group receiving maintenance therapy, 11 of 20 patients remained in clinical

remission at 12 months of therapy, whereas 8 patients required adjustment of IFX doses or intervals. Among the 11 children who were in clinical remission and receiving maintenance therapy without dose adjustment, 8 experienced relapse within 12 months after IFX maintenance therapy was stopped. Overall, the relapse rates after IFX induction or maintenance therapy was stopped were 75% and 72%, respectively.

Conclusions: These data indicate that IFX is efficacious in controlling severe pediatric CD; however, to induce and maintain clinical remission, repeated IFX infusions are required, with a need for dose adjustment in a substantial number of patients. *JPGN* 46:293–298, 2008. **Key Words:** Crohn disease—Mucosal healing—Infliximab. © 2008 by European Society for Pediatric Gastroenterology, Hepatology, and Nutrition and North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition

Treating inflammatory bowel diseases (IBD) is a major challenge for clinicians because no curative therapy exists (1,2). During the past 20 years, marked progress has been made in the treatment of IBD, resulting in the development of new therapeutic concepts and drugs. A major step forward in the care for adult and pediatric patients with IBD, mainly Crohn disease (CD), was the introduction of biological therapies directed against cytokines or soluble factors (3). Several randomized placebo-controlled studies clearly showed that the biological drug infliximab (IFX; Remicade), directed

against soluble and membrane-bound tumor necrosis factor- α , is highly efficacious in improving the clinical course in adult and pediatric CD patients (4–10). Clinical improvement and remission occurs most often within 1 or 2 weeks after administration. Follow-up endoscopies showed that a decrease in the disease activity index after 1 IFX infusion was paralleled by a marked improvement of inflammatory mucosal lesions, resulting most often in healing of mucosal ulcerations (11,12). This observation indicates that therapy based on antitumor necrosis factor has the potential to disrupt the inflammatory cycle within the intestinal mucosa, allowing optimal disease control. In contrast to IFX, steroids fail to induce mucosal healing (13), despite excellent anti-inflammatory effects in CD, and relapse rates after steroid discontinuation are high.

The potential of IFX not only to induce but also to maintain remission is now well studied in adult and

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pediatric CD cohorts (6,12,14). Recent data from the pediatric REACH study indicate that after 1 year of scheduled IFX therapy with concurrent immunomodulator medication, 29 of 52 patients with CD remained in remission without IFX dose adjustment (14). However, there are scant data on the clinical course of pediatric CD once IFX medication is stopped, and we thus do not know how long patients with CD should continue to receive IFX maintenance therapy. Given the recent reports of a particularly aggressive and most often lethal form of a hepatosplenic T cell lymphoma in 8 adolescent or young adult patients with CD receiving azathioprine/6-mercaptopurine (AZA/6-MP) and IFX bithery (15,16), there are major concerns about the safety of this now commonly used bithery treatment scheme (IFX–AZA/6-MP). Therefore, it is most helpful to understand whether successful IFX therapy can profoundly stabilize the course of severe pediatric CD, allowing IFX infusions to be discontinued after a well-defined treatment interval. To address this question in an indirect way, we analyzed in an open manner the outcome in 36 pediatric patients with CD once IFX medication was stopped, with a follow-up time of at least 12 months. All of the patients initially responded to IFX induction therapy with clinical remission and received maintenance stable immunomodulator treatment once IFX was stopped.

PATIENTS AND METHODS

A retrospective chart analysis of our combined IBD program database (Necker-Enfants Malades and Robert Debré Hospital) allowed us to identify a total of 38 consecutive pediatric patients with clear-cut CD who were treated with 3 or more doses of IFX for a particularly severe disease course (steroid dependency/resistance and/or failure of immunomodulator therapy) during the period 2000 to 2004. All of the patients were followed up for at least 12 months after IFX was discontinued. Diagnostic studies (upper gastrointestinal series with small bowel follow-through, barium enema or abdominal computed tomography, upper and lower gastrointestinal endoscopy during general anesthesia) was completed in all 38 children. The diagnosis of CD was made according to the criteria defined by Gower-Rousseau et al (17). Infectious diseases, such as tuberculosis or a *Yersinia* infection, were systematically ruled out, as were immunodeficiencies or septic granulomatosis. The patients' characteristics (sex, disease location, presence of granulomas, presence of anti-*Saccharomyces cerevisiae* antibodies, surgery) are shown in Table 1. Crohn disease was diagnosed at a mean age of 10.7 ± 2.2 years, and IFX therapy was started 3.1 ± 2.3 years after diagnosis (range 4 months–6.4 years, median 29 months). Infliximab (5 mg/kg if not stated otherwise) was administered intravenously over 3 to 4 hours. All of the patients received antihistaminic and hydrocortisone premedication, and during IFX administration all of the patients received cardiac and blood pressure monitoring.

Disease activity was monitored by use of the Harvey-Bradshaw index (HBI) (18). Clinical remission was defined by

TABLE 1. Clinical characteristics of 36 patients with CD

	Group 1 IFX induction scheme	Group 2 IFX maintenance scheme
Age at diagnosis, y	10.3 ± 2.5	10.7 ± 2.2
Sex (M – F)	9 (56%)–7 (44%)	12 (60%)–8 (40%)
Duration of disease at IFX introduction, y	3.7 ± 2.9	3.0 ± 2.2
Range, y	1.2–8.6	0.5–7.9
Luminal CD (%)	13 (81)	14 (70)
Perianal fistulizing CD (%)	3 (19)	6 (30)
Disease site		
Ileal involvement	1	2
Colonic involvement	4	8
Ileocolonic involvement	11	10
Granuloma (%)	11 (69)	15 (75)
AZA/6-MP before IFX therapy		
Failure	13	15
Intolerance	0	2
Methotrexate before IFX therapy		
Failure	1	1

an HBI below 5. A relapse was defined by an increase in the HBI of at least 3 points or an HBI of 5 or above. Mucosal healing was defined as disappearance of all inflammatory lesions, including ulcerations with a macroscopically normal mucosa, in keeping with the recent subanalysis of the ACCENT 1 trial (12). The presence of anti-IFX antibodies was tested before each IFX infusion, as recently described (19).

Analysis of the data in this study was both descriptive and analytic. Statistical analysis for the comparison of the qualitative variables was carried out by the χ^2 test or the Fisher exact test. $P < 0.05$ was regarded as significant.

RESULTS

Efficacy of IFX Induction Therapy

Thirty-eight consecutive pediatric patients with CD with a severe disease course were treated with an induction scheme of 3 IFX infusions. The indications for the introduction of IFX were steroid dependency ($n = 20$) or steroid resistance ($n = 11$) combined with failure of, or intolerance to, AZA/6-MP ($n = 30$) or methotrexate ($n = 2$). Induction therapy consisted of 3 IFX infusions (5 mg/kg) at day 0, day 14, and day 45 in all of the children. At 3 months, after 3 IFX infusions, 36 of 38 children (95%) were in full clinical remission (HBI < 5), whereas in 2 patients (5%) remission did not occur (HBI ≥ 5). These 2 patients were considered to be primary IFX nonresponders, and they were excluded from the following analyses.

The remaining 36 patients were separated into 2 subgroups on a historical basis, inasmuch as pediatric patients with CD in our centers received only an initial induction scheme of 3 IFX infusions before 2002. Therefore, the first 16 patients of this series received no further IFX infusions beyond this induction therapy,

whereas the next 20 patients received a maintenance schedule of IFX infusions every 8 weeks for a total of 12 months.

Clinical Course Over 12 Months After IFX Induction Therapy

All 16 patients received maintenance immunomodulatory therapy after IFX was discontinued, and they were followed up for at least 12 months. Unfortunately, within 12 months (mean 5.2 months, median 4 months) after IFX induction therapy, 12 of 16 patients (75%) experienced massive relapse, requiring surgery (7 of 12) and/or repeated steroid therapy (9 of 12), followed by IFX retreatment in 7 patients. Clinically manifest relapse occurred in 8 patients within 6 months after IFX medication was discontinued. By contrast, 4 of 16 patients (25%) remained in clinical remission for as long as 24 months after IFX induction therapy with a single immunomodulator (Fig. 1).

Efficacy of IFX Maintenance Therapy for 1 Year

After induction therapy, 20 patients with CD received maintenance IFX infusion therapy on a scheduled 2-month basis for 1 year (Fig. 2). During this maintenance therapy period, IFX doses had to be doubled and/or the intervals between infusions had to be shortened from 8 to 6 weeks in 8 of 20 patients (40%) because of a loss of response. These patients, who crossed over to a different treatment regimen because of a loss of clinical response, were in the follow-up considered to be nonresponders. Six of the 8 children showing a loss of response regained a clinical response to increased IFX doses and/or reduced administration intervals. One child had to be excluded from further analysis at the 6-month visit because she experienced a

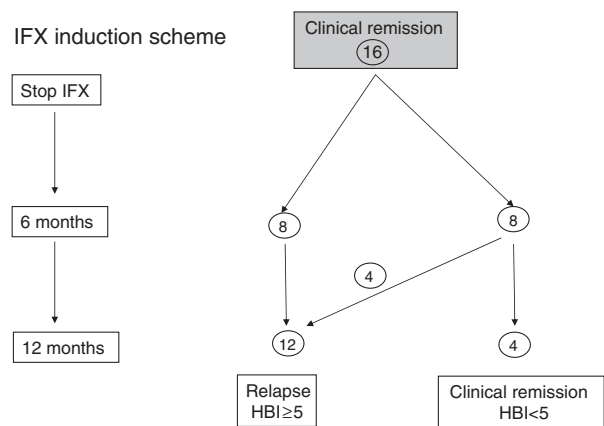


FIG. 1. 12-month follow-up after discontinuance of IFX in 16 patients with CD who experienced clinical remission with IFX induction therapy; 8 children experienced relapse (HBI ≥ 5) within the first 6 months after IFX infusions were stopped.

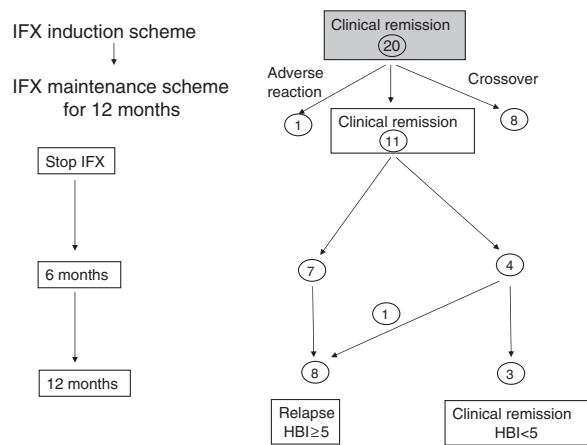


FIG. 2. Clinical response to IFX maintenance therapy over 12 months; 11 children stayed in clinical remission during scheduled IFX maintenance therapy, whereas 8 children crossed over to an intensified IFX treatment schedule (dose increase/shorting of infusion intervals). During the 12-month follow-up interval after IFX maintenance therapy was stopped, 8 children experienced relapse.

severe adverse reaction to IFX. Therefore, at 6 and 12 months, respectively, the clinical remission rates were 16 of 19 (84%) and 11 of 19 (58%).

Clinical Course Over 12 Months After Discontinuation of IFX Maintenance Therapy

In the remaining 11 patients who were in complete clinical remission after 12 months of maintenance IFX therapy, IFX infusions were stopped and patients were followed up for 12 months. Eight of the remaining 11 patients experienced clinical relapse within 12 months after IFX withdrawal despite continued immunomodulator therapy (mean 4.1 months, median 3 months). Subsequently, 2 patients required surgery, and in 9 patients, IFX was reintroduced. Only 3 patients of the initial 20 children remained in clinical remission beyond the 12-month follow-up interval after IFX maintenance therapy was discontinued.

Adverse Reactions and Formation of Anti-IFX Antibodies

All of the patients received premedication (dexchlorpheniramine plus hydrocortisone) before receiving IFX infusions, and all of the patients were receiving concomitant immunomodulator medication (AZA [36 patients] or methotrexate [2 patients]). Adverse reactions or side effects during IFX administration were observed during 3 infusions (3 of 235, 1%), leading to the discontinuation of IFX in 1 patient during the fourth infusion. This patient showed an acute anaphylactic reaction with low blood

pressure and tachycardia, rapidly stabilized by intravenous fluid resuscitation. The other patients showed skin flash, mild dyspnea, or tachycardia without hypotension. Two of the 3 patients who experienced IFX side effects had positive test results for the presence of anti-IFX antibodies, including the patient with the anaphylactic reaction. No infectious complications were recorded in this population during IFX therapy except for 1 mild reactivation of a herpes zoster infection.

High titers of anti-IFX antibodies (>40%) were present in 9 of 29 patients (31%), whereas negative results were observed in the remaining 20 of 29 patients. During the years 2000 to 2002, not all of the patients treated with IFX were routinely tested for the presence of anti-IFX antibodies. Therefore, the anti-IFX antibody status is unknown in 9 patients. The 2 children who did not respond to IFX induction therapy had positive anti-IFX antibodies, compared with 7 of 27 tested children who were in complete clinical remission at month 3 of IFX therapy. Also of interest, 6 of 8 children receiving maintenance IFX therapy who required increasing IFX doses and/or reduced perfusion intervals had positive test results for anti-IFX antibodies.

Mucosal Healing After IFX Induction Therapy

Of this cohort, 13 patients underwent control endoscopy at month 3 (after 3 infusions of IFX). Complete disappearance of mucosal ulcerations was observed in 6 of 13 children, with marked improvement of mucosal lesions in an additional 4 patients. Three children still showed significant mucosal ulcerations. Of interest, 2 of these patients with deep ulcerations shown by control endoscopy remained in remission for 8 and 12 months, respectively, after IFX therapy was stopped. The third child was 1 of the 2 primary IFX nonresponders.

DISCUSSION

IFX is a potent anti-inflammatory drug with profound immunoregulatory properties. Our study confirms previous reports in pediatric CD populations that IFX obtains clinical remission or at least improvement in the majority of patients, and this most often occurs within a couple of days after IFX infusion (8–10). In the present study, we independently confirmed previous reports of American and European pediatric IBD centers (8–10) in showing that induction therapy with 3 doses of IFX induces complete clinical remission in >80% of pediatric patients with CD. In addition, IFX maintenance therapy based on a scheduled 2-month administration was efficacious in maintaining clinical remission in the majority of patients. These data are in keeping with the recent REACH study (14): this multicenter, randomized, open-label study showed for the first time in a prospective

manner that scheduled IFX maintenance therapy is effective in pediatric patients with CD. At the end of the study protocol (54 weeks), a little more than half of the patients receiving IFX maintenance therapy were in clinical remission, without dose adjustment. Even though our study was retrospective and in a smaller cohort, the data presented in our analysis are comparable to the results of the REACH study in that the majority of patients initially responded to IFX maintenance therapy, but with time almost half of our patients with CD showed a loss of response to IFX during maintenance therapy, despite concomitant treatment with immunomodulators.

The development of anti-IFX antibodies is a major factor responsible for the loss of efficacy of IFX and for the occurrence of immunoallergic infusion reactions. In the present study, we observed a sensitization rate of about one third of patients despite premedication and concomitant immunosuppression. This is within the range previously reported in different adult and pediatric studies (20–22). However, in the REACH study, this rate was markedly lower. It must be noted that the number of patients with inconclusive results (due to the presence of circulating IFX) was almost 80% in the REACH study, complicating interpretation of the results. In our analysis, the number of patients with high titers of anti-IFX antibodies was significantly higher in the group of children who did not respond to IFX and in the group who required increasing doses of IFX during maintenance therapy.

A major question is related to the potential of IFX to completely interrupt the inflammatory process, theoretically allowing the induction of long-term remission even after IFX maintenance therapy is discontinued. In an ideal world, one could hope that this type of therapy allows us to “put the counter back to zero.” This may come in the form of a complete disappearance of all mucosal inflammatory lesions (mucosal healing) and may translate into long-lasting clinical remission. To address this point, we analyzed in the present study the clinical course of 36 pediatric patients with severe CD during a 12-month follow-up interval after IFX medication was stopped. All of the children were IFX responders and experienced clinical remission while receiving IFX induction therapy. The 36 patients were separated into 2 different groups, 1 receiving IFX only as induction therapy, the other receiving IFX over 12 months as maintenance therapy. We observed in both groups, despite an excellent clinical response to IFX, that the majority of patients (75% and 72%, respectively) experienced relapse within 12 months after IFX therapy was stopped, whereas immunomodulator treatment continued unchanged. This was in keeping with our previous study on a different cohort of 21 children with CD (8), a prospective analysis of the response to IFX induction therapy, in which 90% of patients experienced relapse within the first year after IFX therapy despite continued immunosuppressive therapy (8). In both studies, the majority of patients experienced relapse within the first

3 months after IFX was stopped, as seen in an HBI above 5 points.

The loss of response to IFX during maintenance therapy—most often caused by the formation of anti-IFX antibodies—and the lack of a long-term anti-inflammatory effect once IFX was stopped is intriguing. This points to a potent immunomodulatory effect of IFX that is downstream from the inflammatory cascade in CD, but certainly not to a curative effect, or at least upstream in the immunological reaction, inasmuch as the overwhelming majority of patients in this study required repeated IFX infusions to maintain clinical remission. Wewer et al (23) recently introduced the term “IFX dependency” because almost half of their patients required additional IFX infusions within 90 days after the discontinuation of IFX to further stabilize their course, in keeping with our data in the present report.

Because long-term clinical remission is dependent on repeated IFX infusions and, in several patients, on increasing IFX doses with time, it is important to address the question of how long patients with CD should be treated with IFX. When this point is considered, not only efficacy data but also safety concerns must be addressed. In the present study, severe adverse reactions during IFX infusions were rare, in keeping with recent reports (14,24) indicating that IFX is generally well tolerated in pediatric patients with CD even after prolonged administration. However, in 1 patient, IFX had to be stopped secondary to an anaphylactic reaction. In addition, massive bacterial complications with fatal outcome under IFX have been reported in both adult and pediatric patients with CD (14,25,26). Even if IFX is immediately well tolerated in general, major concerns arise about its long-term safety, such as the occurrence of malignancy as discussed above.

Infliximab is a useful and powerful drug in the induction and maintenance of remission in pediatric CD. However, with the increasing use of IFX, we discover new limitations of this drug in the form of IFX dependence or IFX resistance in a substantial number of patients. Safety concerns are primary for all physicians, particularly pediatricians, especially when long-term maintenance therapy with a potent immunomodulator is considered for a severely sick child with CD. Therefore, before a long-term use of IFX over years as maintenance therapy for pediatric CD—already a common practice in many centers—can be recommended, additional evidence-based data, including safety data from large multicenter studies, are needed.

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