Pediatric inflammatory bowel disease: Diagnostics, treatment and psychosocial consequences
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CHAPTER 4

The duration of effect
of infliximab maintenance treatment in
pediatric Crohn’s disease is limited

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ABSTRACT

Background: Infliximab (IFX) is effective for induction and maintenance of remission in children with moderately to severely active Crohn’s disease (CD).

Objective: To evaluate the long-term efficacy of IFX treatment in pediatric CD.

Methods: In this observational, multicenter study, all pediatric CD patients in the Netherlands treated with IFX from October 1992 to November 2009 and with minimal follow-up of three months since start of IFX, were studied.

Results: 152 CD patients (81 M; median age at start of IFX 15.0 years (IQR 13.1-16.4)) received a median number of 10.5 IFX infusions (IQR 6-21). Median follow-up after start of IFX was 25 months (IQR 13-40). Kaplan-Meier analysis showed that the cumulative probability of losing response to IFX in patients who initially required repeated infusions, was 13%, 40%, and 50% after 1, 3 and 5 years, respectively. Seventy-four patients (49%) needed dose adjustments, with a median time to any adjustment of six months.

Conclusions: Duration of effect of IFX is limited since 50% of patients on IFX maintenance treatment lose their therapeutic response after five years. Dose adjustments after start of IFX are frequently needed to regain therapeutic benefit. These findings emphasize the need for effective, long-term treatment strategies for pediatric CD.
INTRODUCTION

Infliximab (IFX; Remicade®) is a chimeric monoclonal antibody (75% human, 25% murine) that binds with high affinity and specificity to tumor necrosis factor-α (TNF-α) (1), a pro-inflammatory cytokine with increased expression in the inflamed intestinal mucosa of children with active Crohn’s disease (CD) (2).

Since the first use of IFX for CD in 1992 in a thirteen-year old girl (3), several small non-randomized, non-placebo controlled studies (4-9) and a randomized multicenter open-label study (10) have demonstrated the efficacy of IFX to induce and maintain clinical remission in children with moderate to severe CD. This biological has greatly improved the therapeutic options for refractory pediatric CD. Although IFX has a good short-term safety profile (9-12), there are concerns about the long-term safety aspects, especially since post-marketing surveillance reported on the occurrence of 18 cases of hepatosplenic T cell lymphoma (HSTCL) (data on file, Centocor). This aggressive form of non-Hodgkin’s lymphoma occurred in predominantly male adolescents and young adults with inflammatory bowel disease (IBD; mostly CD) who had been treated with anti-TNF-α and thiopurines (13).

To date, data on long-term efficacy of IFX in pediatric CD are still limited. A recent study by Hyams et al. (14) showed that during the third year of IFX maintenance therapy, 33% of patients had sustained remission (defined as clinically inactive disease not requiring corticosteroids or surgery). In addition, our previous study (9) demonstrated that sustained clinical response after cessation of IFX treatment or on IFX maintenance therapy was seen in 70% of patients after a mean follow-up of 41 months.

To avoid exposure and toxicity in the patients who will not benefit from IFX therapy in the long-term, it is important to find predictors of prolonged response. Episodic treatment has been associated with higher relapse rates compared to scheduled maintenance treatment both in adults and children (12,15). Other clear risk factors for IFX failure have not been identified in children, except for the possible influence of disease duration before start of IFX treatment. Two pediatric studies have reported prolonged duration of response after IFX treatment when the drug was initiated early in the disease course (4,7), but we were not able to confirm this difference in our previous study (9).

The primary aim of this study was to evaluate the long-term efficacy of IFX treatment in a national cohort of pediatric CD patients treated with IFX. The secondary aim was to examine whether clinical factors, such as gender, age at diagnosis, disease location and disease duration before start of IFX, were associated with treatment outcome.
MATERIALS AND METHODS

Patients
All pediatric CD patients treated with IFX since 1992 by pediatric gastroenterologists in the Netherlands were reviewed. After the appearance of a national consensus guideline on the indications and use of IFX in children with refractory CD, a database was initiated in 2002 with the purpose to audit IFX treatment given by pediatric gastroenterologists in the Netherlands. Patients who received IFX in the period 1992–2002, were retrospectively included in the database (n=22).

Patients were included in this study when IFX was started before the age of 19 years and follow-up was at least three months after initiation of IFX treatment. Patients who did not receive a three-dose induction scheme at 0, 2 and 6 weeks and/or were treated episodically, were excluded.

Data on patient characteristics, disease history, previous and concomitant treatments were recorded. In addition, number and schedule of IFX infusions, outcome of IFX treatment, adverse events, surgery and treatment in case of IFX failure were extracted from the medical records. Data were collected until November 2009.

Definitions
The outcome of IFX treatment was defined as prolonged response, IFX requirement, loss of response, or non-response. Patients who maintained good clinical response minimally three months after IFX treatment stopped, were classified as having a prolonged response. Good clinical response was based on the judgment of the treating pediatric gastroenterologist. IFX requirement indicated that repeated IFX infusions were needed to maintain good clinical response. Adjustments in treatment schedule (dosage increase up to 10 mg/kg and/or shortening of the interval between two infusions) were allowed in these patients. Patients with loss of response had an initial good clinical response to IFX maintenance treatment, but eventually there was a need for surgery or withdrawal of IFX (including patients with recurrent allergic reactions despite prophylaxis) and switch to other medical therapy. Finally, non-response was defined as no clinical response to a three-dose IFX induction scheme and withdrawal of IFX after three infusions in total. Treatment outcome was considered successful in case of prolonged response or IFX requirement.

Statistical analysis
Data were collected and analyzed in SPSS (version 15.0, SPSS, Inc., Chicago, IL). Descriptive statistics were calculated as percentages for discrete data and medians with interquartile ranges (IQR) for continuous data. Kaplan-Meier analysis was used to estimate the cumulative probability of losing response to IFX treatment over time. Time to event was analyzed from the date of IFX initiation until the date of loss of response to IFX, or last known follow-up.
To analyze predictive factors of IFX failure among categorical baseline characteristics (i.e. gender, disease location at diagnosis, initiation of IFX within one year after diagnosis, previous bowel surgery), univariate analyses with log-rank test were used. Multivariate Cox proportional hazards regression was used to identify independent variables predictive of IFX failure. The proportional hazards assumption was checked using log-minus-log survival plots. To assess the relation between treatment outcome and adverse events, Fisher’s exact test was used. All reported p-values are two-sided. P-values < 0.05 were considered significant.

RESULTS

Patient characteristics
Between October 1992 and November 2009, 188 pediatric patients in the Netherlands were treated with IFX in thirteen hospitals. Thirty-six patients were excluded because of the following reasons: follow-up < 3 months (n=6), no administration of a three-dose induction scheme (n=26), episodic treatment (n=3) and lost to follow-up (n=1).

Characteristics of the 152 included patients are shown in Table 1. The median age at start of IFX treatment was 15.0 years (IQR 13.1–16.4) after a median disease duration of 1.8 years (IQR 0.8–3.0). All patients but five were refractory to conventional treatment. These five patients received first-line IFX therapy because of severity of colonic disease at presentation (n=1)(16), perianal fistulas in the presence of juvenile idiopathic arthritis (n=1) and complex perianal fistulas at presentation (n=3).

The majority of patients (n=133) received a three-dose induction scheme at 0, 2 and 6 weeks followed by maintenance treatment. Sixteen patients (11%) received an induction scheme only. In three patients (2%) IFX was stopped after the induction scheme, but treatment was restarted when disease relapsed.
Table 1. Patient characteristics at start of infliximab treatment (n=152)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (male), no. (%)</td>
<td>81 (53.3)</td>
</tr>
<tr>
<td>Age at start treatment (yr), median (IQR)</td>
<td>15.0 (13.1–16.4)</td>
</tr>
<tr>
<td>Disease duration before start of infliximab (yr), median (IQR)</td>
<td>1.8 (0.8–3.0)</td>
</tr>
<tr>
<td>Disease location at diagnosis, no. (%)</td>
<td></td>
</tr>
<tr>
<td>Small bowel</td>
<td>13 (8.6)</td>
</tr>
<tr>
<td>Colon</td>
<td>43 (28.3)</td>
</tr>
<tr>
<td>Both</td>
<td>95 (62.5)</td>
</tr>
<tr>
<td>Isolated perianal fistulas</td>
<td>1 (0.7)</td>
</tr>
<tr>
<td>Previous surgery, no. (%)</td>
<td></td>
</tr>
<tr>
<td>Bowel surgery</td>
<td>32 (21.1)</td>
</tr>
<tr>
<td>Fistula correction</td>
<td>16 (10.5)</td>
</tr>
<tr>
<td>Both</td>
<td>15 (9.9)</td>
</tr>
<tr>
<td>Previous medication, no. (%)</td>
<td></td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>136 (89.5)</td>
</tr>
<tr>
<td>Exclusive enteral nutrition</td>
<td>63 (41.4)</td>
</tr>
<tr>
<td>Thiopurine</td>
<td>143 (94.1)</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>38 (25.0)</td>
</tr>
<tr>
<td>5-Amino-salicylic acids</td>
<td>99 (65.1)</td>
</tr>
<tr>
<td>Indication for infliximab, no. (%)</td>
<td></td>
</tr>
<tr>
<td>Refractory luminal disease</td>
<td>105 (69.1)</td>
</tr>
<tr>
<td>Refractory luminal disease and perianal fistulas</td>
<td>19 (12.5)</td>
</tr>
<tr>
<td>Refractory luminal disease and growth retardation</td>
<td>12 (7.9)</td>
</tr>
<tr>
<td>Perianal fistulas</td>
<td>11 (7.2)</td>
</tr>
<tr>
<td>First line</td>
<td>5 (3.3)</td>
</tr>
</tbody>
</table>

IQR= interquartile range.

Outcome of IFX treatment

Median duration of IFX treatment was 16 months (IQR 7–34, range 2–132). In total, 2291 infusions were administered (median 10.5, IQR 6–21, range 3–86). Patients were followed for a median of 25 months (IQR 13–40, range 3–132) after start of IFX treatment, with 20 patients (13%) having a follow-up of more than five years.

Analysis of the entire cohort demonstrated that 15 patients (10%) had a prolonged response of at least three months after cessation of IFX therapy, 92 patients (61%) required repeated IFX infusions, while 40 patients (26%) had loss of response and 5 patients (3%) had no initial response to treatment.
Figure 1 shows follow-up of pediatric CD patients treated with IFX. The number of patients on IFX maintenance treatment decreased during the years due to discontinuation of treatment or reaching the end of the follow-up period. The majority of prolonged responders was treated with IFX because of isolated fistulizing disease (9/15), and received a three-dose induction scheme only (10/15). In the five remaining patients, IFX was stopped because of good clinical effect. CRP levels three to seven months after cessation of IFX were available in nine patients, with a median level of 4 mg/L (IQR 3–10). Seven patients (47%) remained in remission during a median follow-up of 18 months (range 3–29 months). IFX was restarted in three out of the eight patients with relapse of disease and this was successful in two of them.

Forty-six percent (42/92) of the patients who required repeated IFX infusions, received concomitant medication at the end of the follow-up period: thiopurines (n=26), methotrexate (n=8), 5-amino-salicylic-acids (n=7) and corticosteroids (n=1). Four of the six patients requiring IFX after five years continued IFX treatment until the end of the follow-up period (range 61–81 months). The remaining two patients lost response after 69 and 101 months, respectively.

Kaplan-Meier analysis showed that the cumulative probability of losing response to IFX in patients who required repeated infusions, was 13% (± 3.1%), 40% (± 5.5%), and 50% (± 9.2%) after 1, 3 and 5 years, respectively (Figure 2).

Adjustments in treatment schedule
Adjustments in treatment schedule at any time during follow-up were made in 74/152 (49%) of the patients. In 28 of the 40 patients who lost response to IFX (70%), an adjustment in treatment schedule was made before it was decided that IFX treatment had failed. Forty out of 92 (44%) patients with IFX requirement needed intensification of treatment, which was temporary in twelve patients. The median time to any adjustment in treatment schedule was six months (IQR 3–11). The timing of adjustments in treatment schedule is displayed in Figure 1.

Fifty-four patients (73%) had initial adjustment with a decreased interval of 4–7 weeks between two infusions, in 16 patients (22%) the initial adjustment was a dosage increase and in two patients both adjustments were made at the same time. In two patients, the sequence of the adjustments was unknown. Eventually, 32 of the 74 patients (43%) needed both a decrease in interval between two infusions and an increase in dosage.
Figure 1. Outcome of infliximab according to duration of treatment in 152 pediatric Crohn's disease patients.

**Time after start infliximab**

**1 year**
- **Infliximab requirement**
  - N=88
  - 39 dosing adjustments
- **Discontinued infliximab**
  - N=34
  - 13 Prolonged response
  - 16 Loss of response, 10 dosing adjustments
  - 5 Non-response, 1 dosing adjustment
- **Follow-up < 1 year**
  - N=30
  - 8 dosing adjustments

**2 years**
- **Infliximab requirement**
  - N=47
  - 21 dosing adjustments (6 this year)
- **Discontinued infliximab**
  - N=16
  - 16 Loss of response, 10 dosing adjustments
- **Follow-up < 2 year**
  - N=25
  - 9 dosing adjustments (1 this year)

**3 years**
- **Infliximab requirement**
  - N=30
  - 16 dosing adjustments (3 this year)
- **Discontinued infliximab**
  - N=5
  - 1 Prolonged response
  - 4 Loss of response, 4 dosing adjustments
- **Follow-up < 3 year**
  - N=12
  - 3 dosing adjustments (1 this year)

**4 years**
- **Infliximab requirement**
  - N=11
  - 5 dosing adjustments (2 this year)
- **Discontinued infliximab**
  - N=2
  - 1 Prolonged response
  - 1 Loss of response, 1 dosing adjustment
- **Follow-up < 4 year**
  - N=17
  - 8 dosing adjustments

**5 years**
- **Infliximab requirement**
  - N=6
  - 2 dosing adjustments
- **Discontinued infliximab**
  - N=1
  - 1 Loss of response, 1 dosing adjustment
- **Follow-up < 5 year**
  - N=4
  - 2 dosing adjustments
Figure 2. Kaplan-Meier analysis of duration of infliximab treatment in pediatric Crohn’s disease patients who initially required repeated infusions.

Clinical predictors of IFX failure
None of the following factors were predictive of IFX failure in univariate analysis (log-rank test): disease location (p=0.75), initiation of IFX within one year after diagnosis (p=0.73), and previous bowel surgery (p=0.26). There was a trend toward a higher risk of IFX failure in females (p=0.063). Since gender did not meet the proportional hazards assumption, we had to perform a stratified multivariate proportional hazards analysis, as displayed in Table 2. Again, we found no independent predictors of IFX failure.
Table 2. Predictors of infliximab failure (i.e. non-response or secondary loss of response) in stratified multivariate Cox proportional hazards regression analysis

<table>
<thead>
<tr>
<th>Predictor</th>
<th>HR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at diagnosis</td>
<td>0.99</td>
<td>0.88 - 1.11</td>
<td>0.86</td>
</tr>
<tr>
<td>Disease location at diagnosis</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Small bowel</td>
<td>1.68</td>
<td>0.38 - 7.40</td>
<td>0.50</td>
</tr>
<tr>
<td>Colon</td>
<td>1.55</td>
<td>0.36 - 6.66</td>
<td>0.55</td>
</tr>
<tr>
<td>Both</td>
<td>0.83</td>
<td>0.40 - 1.70</td>
<td>0.61</td>
</tr>
<tr>
<td>Initiation of IFX within 1 yr after diagnosis</td>
<td>1.41</td>
<td>0.61 - 3.25</td>
<td>0.42</td>
</tr>
<tr>
<td>Previous bowel surgery</td>
<td></td>
<td></td>
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</tbody>
</table>

Analysis was stratified according to gender, HR= hazard ratio, CI= confidence interval, IFX= infliximab.

Treatment in case of IFX failure
Primary or secondary IFX failure was seen in a total of 45 patients. In most patients (n=35) maintenance treatment with an immunomodulator, including thiopurines (n=20) or methotrexate (n=15), was continued or restarted. Twenty-four patients underwent surgery (53%): bowel surgery in 19 patients, fistula correction in two patients and both bowel surgery and fistula correction in three patients. The median time between start of IFX treatment and surgery was 15.5 months (IQR 4–24). Despite the need for surgery, IFX was continued in twelve patients: eight were still being treated with IFX at the end of the follow-up period, three patients eventually needed other medication and one patient was unsuccessfully treated with adalimumab and switched back to IFX treatment. There was a great variety in other treatment strategies used after IFX failure: adalimumab (n=20), corticosteroids (n=6), exclusive enteral nutrition (n=4) and/or restart of IFX (n=5). This latter treatment strategy was successful in two patients, but they required IFX again at the end of the follow-up period. A small minority of patients was treated with certolizumab (n=2), thalidomide (n=1) or anti-CD3 (n=2).

Adverse events
Among the entire cohort of patients, 17 patients (11%) experienced a type 1 allergic reaction during infusion. Reactions resolved spontaneously or after administration of intravenous corticosteroids and/or an antihistaminic. Treatment with IFX had to be discontinued in three patients because of recurrent allergic reactions despite prophylaxis. In total, 25 patients (16%) developed a mostly mild infection during treatment with IFX (e.g. gastroenteritis, upper respiratory tract infection, pneumonia, herpes infection, fungal infection, Clostridium colitis). However, one patient developed uncontrollable bacterial sepsis five months after start of IFX and died (previously published by de Ridder et al. (17). Another serious infection (severe reactivation of EBV infection) was seen in a twelve-year
old patient, which required temporary discontinuation of IFX treatment. A third patient refused further treatment with IFX because of a range of side effects (frequent upper respiratory tract infections, headache and mood swings). There was no significant difference in occurrence of infections between successfully treated patients and patients in whom IFX therapy failed (14% vs. 22%; p=0.24). Twelve patients (8%) reported a wide variety of skin eruptions (e.g. eczema, psoriasiform lesions) during the course of IFX treatment, but there was no need for discontinuation of treatment. There was no significant relation between the occurrence of skin eruptions and treatment outcome (8% in successfully treated patients; 9% in patients in whom IFX therapy failed; p=0.75). No gender differences were found in the occurrence of allergic reactions, infections and skin eruptions (p=1.0; p=0.38; p=1.0).

One patient developed a basal cell carcinoma on the scalp 27 months after start of IFX therapy. Drug-induced lupus was seen in one patient, who discontinued treatment and switched to adalimumab. No other autoimmune phenomena were observed. Serum sickness-like disease, demyelination and heart failure were not observed in this cohort of patients.

DISCUSSION

Our study describes the longest follow-up until now of a large, multicenter cohort of pediatric CD patients receiving induction with IFX followed by scheduled maintenance treatment in the majority of patients. Although IFX treatment is effective in children with refractory CD, our study shows that the therapeutic effect decreases over time with loss of response in 50% of patients who initially required repeated infusions, after five years. Adjustments in treatment schedule, decreased intervals and/or dosage increases, were required in 49% of the patients in order to maintain clinical response, with a median time to any adjustment of six months.

Recently, another large multicenter cohort study reported on the long-term outcome of IFX maintenance therapy in pediatric CD (14). This study showed that 33% of patients discontinued IFX treatment after three years due to several reasons (elective, loss of response, primary non-response, allergy). The results on frequency and timing of dose adjustments were comparable with our results. Since our study only examined IFX discontinuation due to loss of response, these outcomes are somewhat difficult to compare. However, it seems that discontinuation of IFX due to loss of response occurred more frequently in our cohort of patients (40% loss of response after three years). An explanation for this difference could be the earlier introduction of IFX in the USA: the median interval between diagnosis and start of IFX was nine months compared to 1.8
years in our study. This probably indicates more severe and complicated disease courses in our patients, which is reflected by the larger proportion of patients who underwent surgery before IFX initiation in our study (21% compared to 6% in the study of Hyams et al.) Another reason for the difference in loss of response could be the higher frequency of concomitant use of corticosteroids (9% at three years of follow-up compared to 1% in our study).

Our study found a trend toward a higher risk of IFX failure in females. Interestingly, male IBD patients seem to have the highest risk of developing HSTCL. It could be hypothesized that male patients achieve higher serum IFX concentrations compared to females. Pharmacokinetic differences have been found in male and female adult IBD patients treated with IFX (19). These findings warrant further investigation. In contrast with two previous studies (4,7), we did not find an association between treatment outcome and disease duration before start of IFX. This may be explained by several factors. In the first study, only one IFX infusion was administered, while all patients in our study received induction with IFX usually followed by scheduled maintenance treatment. Current CD treatment guidelines (20-21) recommend a three-dose induction scheme and scheduled maintenance treatment, indicating that a single infusion is less effective for maintenance of response. In the second study, treatment effect was determined already after 18 weeks, while our study assessed treatment outcome after a median of 25 months. In addition to disease duration, disease location has been suggested as a predictor of response to IFX. Two adult studies have shown that patients with isolated colonic disease were more likely to respond to IFX, at least on the short term (22-23). In our cohort, we did not find a relation between disease location and treatment outcome, which might have been caused by differences in distribution of disease locations between adults and children (24). A recent study demonstrated that adult patients with objective evidence of inflammation (high CRP level and/or mucosal lesions at endoscopy) had the best clinical results with IFX (25). These factors were not assessed in our study.

Infections and infusion reactions were the most frequently observed complications of IFX treatment in our study. Infections were seen in 16% of patients and were mild, except in two patients. Allergic reactions during IFX therapy occurred in 11% of our patients, which is comparable to previous reports (9,26). One young man developed a basal cell carcinoma on the scalp at 18 years of age, 27 months after start of IFX therapy. Before IFX monotherapy, he was treated with azathioprine and methotrexate. Non-melanoma skin cancer (NMSC) has been reported before in adult IBD patients on IFX treatment (18,27-29). A recent study showed that the increased risk for NMSC was especially associated with thiopurine use, but also, to a lesser extent, with biologic treatment (30).

Hepatosplenic T cell lymphoma was not observed in our cohort; our patient population is relatively small and follow-up too short to detect this extremely rare complication. The alarming effect that reporting of HSTCL had on pediatric gastroenterologists probably
caused a decrease in the concomitant use of thiopurines after initiating IFX therapy. In our study, only 28% of patients, who required repeated infusions, received concomitant thiopurines, compared to 64% of the patients in our previous study (9).

Our data should be interpreted in the context of the following limitations. First of all, our study is observational and thus a reflection of daily practice. Decisions concerning adjustments in treatment schedule or discontinuation of IFX treatment were based on the judgment of the pediatric gastroenterologist and did not follow a standardized protocol. Since different schedules for patient visits were used, it was not possible to use the Pediatric Crohn’s Disease Activity Index (PCDAI) or other clinical scores to determine disease activity at set time points. Furthermore, there could be an overlap between patients with a prolonged response to IFX and IFX requirement. The majority of prolonged responders was treated with IFX before pediatric treatment guidelines were available and therefore only received a three-dose induction scheme. Current treatment guidelines do not recommend stopping successful IFX treatment, which has resulted in a decreasing number of prolonged responders in the last two years of our study. Vice versa, it was not routinely attempted to stop IFX in patients who required repeated infusions. Seven out of 92 patients (8%) with IFX requirement received IFX every 10 or 12 weeks at the end of the follow-up period. It is possible that these patients would have had a prolonged response after cessation of IFX. In the remaining 85 patients the risk of flaring was probably considered too high, which is supported by the finding that 46% of these patients required an adjustment in treatment schedule. Another limitation of our study is the absence of data on the formation of antibodies against IFX. Previous adult and pediatric studies have shown that the development of these antibodies is associated with a reduced duration of response to IFX treatment (31-32). We are also unaware of the effect of changes in concomitant treatment during IFX on treatment outcome. Finally, our study does not include pediatric CD patients older than 16 years whose treatment was initiated by an adult gastroenterologist. However, there is no reason to assume that these patients are different from patients treated by pediatric gastroenterologists.

In conclusion, the present study underlines that IFX is an effective therapy in children with refractory CD. However, there are concerns regarding the durability of long-term IFX maintenance treatment, as 50% of patients on IFX maintenance treatment lose their initial therapeutic response after five years. Dose adjustments after start of IFX are frequently needed to regain therapeutic benefit. In contrast to previous studies, loss of response was not found to be associated with disease duration or disease location. These findings emphasize the need for effective long-term treatment strategies for pediatric CD,
as well as the need for predictors of response to IFX treatment to select the most suitable patients for this treatment. This will prevent exposure and toxicity in patients who will not benefit from IFX.
REFERENCES


