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Less Anti-infliximab Antibody Formation in Paediatric Crohn Patients on Concomitant Immunomodulators

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ABSTRACT

Objectives: To evaluate the effect of immunomodulators on formation of antibodies to infliximab (ATI) in paediatric patients with Crohn disease (CD) and the association of ATI and loss of response.

Methods: Retrospective multicentre observational study (January 2009–December 2014) among Dutch children with CD treated with infliximab (IFX). ATI formation was analysed with Chi-square test and time-to-ATI formation with Kaplan-Meier and log-rank test.

Results: A total of 229 children were identified. ATIs were measured in 162 patients (70.7%) and 25 (15%) developed ATIs: 6 of 62 (10%) on continuous combined immunosuppression (CCI), 11 of 81 (14%) on early combined immunosuppression (ECI), and 8 of 19 (42%) on IFX monotherapy. ATI formation was higher in patients on IFX monotherapy compared to CCI ($P = 0.003$) and ECI ($P = 0.008$), whereas no significant difference was found between CCI and ECI. Sixteen out of 25 patients (64%) with ATIs had loss of response, compared with 32 of 137 patients (19%) without ATIs ($P < 0.00002$, log rank 0.02). Among patients treated with ECI, 10 of 55 (18%) developed ATIs within the first 12 months, compared to 1 of 26 (4%) after more than 12 months.

Conclusions: In children with CD combination therapy is associated with significant reduction of antibody formation and prolonged effectivity compared to IFX monotherapy. ECI for at least 12 months, followed by IFX monotherapy, may be an equally effective alternative to CCI.

Key Words: antibodies to infliximab, antitumour necrosis factor, inflammatory bowel disease

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What Is Known

- One of the reasons for loss of response to infliximab in paediatric Crohn disease is development of antibodies to infliximab (ATIs).
- Combining infliximab with an immunomodulator has been shown to reduce antibody to infliximab formation in adults, but there are safety concerns (lymphoma risk).

What Is New

- The risk of antibody to infliximab formation is higher in children not using concomitant immunomodulation.
- Antibody to infliximab formation is unlikely to happen after 12 months of combined therapy.
- Loss of response is strongly associated with antibody to infliximab formation.

What is the impact on clinical practice?

- Although the use of an immunomodulator in combination with infliximab is associated with less ATI formation, uncertainty remains on the optimal duration of combination therapy in the face of lymphoma risk.

Crohn disease (CD) is a chronic inflammatory disease of the gastrointestinal tract. The incidence of CD in children is increasing worldwide, ranging from 2.5 to 11.4 per 100,000 (1). Twenty-five percent to 30% of patients present before the age of 20 years (2), and these young patients are more likely to have severe disease when compared to adult-onset CD, with an increased frequency of periods with active disease (3) and a particular risk for growth failure and delayed puberty (4). Exclusive enteral nutrition (EEN) is recommended as first line therapy to induce remission according to the ECCO/ESPGHAN guidelines with steroids remaining as an alternative if EEN is not an option (1,5). In addition to that, both thiopurines and methotrexate are used to maintain remission (1,6). Infliximab (IFX, Remicade), a chimeric antitumour necrosis factor monoclonal antibody, is proven to be effective in inducing and maintaining remission in patients refractory or intolerant to prior optimized immunomodulator therapy (7), or in children with active perianal fistulizing disease (8). Unfortunately, duration of effect of IFX therapy in paediatric CD is limited due to loss of response (LOR). Two retrospective studies conducted in paediatric IFX patients, described LOR in

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respectively half of patients after 5 years (9) or an LOR rate of 2% to 6% per year over 5 years in patients who experienced complete response (10). One of the reasons for LOR to IFX is development of antibodies to IFX (ATIs) that neutralize the drug (11,12), which develop in 7% to 12% of adult patients receiving regularly scheduled maintenance infusions (13,14). Combining IFX with an immunomodulator such as thiopurines or methotrexate has been shown to reduce the risk of antibody formation directed against IFX (12,13,15,16). The SONIC trial (17), in which adult patients with CD were included who were naïve to both immunomodulators and IFX, has demonstrated that combination therapy is significantly superior to either medication alone in maintaining remission. In addition, several studies with adult patients with inflammatory bowel disease showed superiority of combination therapy (18,19). The primary aim of the present study was to evaluate whether cotreatment with immunomodulators reduces formation of antibodies to IFX in paediatric CD and, secondary, if LOR is associated with ATI formation. Furthermore, the optimal duration of combination therapy was explored.

METHODS

Methods are available online as Supplemental Digital Content 1 (*http://links.lww.com/MPG/A915*).

RESULTS

Patient Characteristics

A total of 229 children with CD treated with IFX between January 2009 and December 2014 were identified. The median age at start of IFX was 14.4 years (interquartile range [IQR] 12.6–15.9), after median disease duration of 12 months (IQR 5–27.1) (Supplemental Digital Content 2, Table, *http://links.lww.com/MPG/A916*). Patients were followed for a median of 32 months (IQR 18.3–53.9) after start of IFX treatment. Group continuous combined immunosuppression (CCI) consists of 86 patients (38%) who continued immunomodulators during IFX treatment throughout the observation period. In the group early combined immunosuppression (ECI, 115 patients [50%]), IFX had been combined with immunomodulators for a median of 6.2 months (IQR 4–15). In most cases in this ECI group (94 patients [82%]) immunomodulating drugs were stopped after an initial period of combination therapy and IFX monotherapy was given afterwards. There were, however, 21 patients treated with alternating combination and monotherapy and those patients were included in the analysis of group ECI. Eventually, 15 of these patients continued on combined therapy and the remaining 6 on IFX monotherapy. Finally, group IFX (IFX monotherapy) consists of 28 patients (12%) with IFX monotherapy throughout the entire observation period. IFX monotherapy was more frequently used during the first years of the observation period while in later years temporary combination therapy (6 months) was often initiated. In the last years, more patients were treated with prolonged combination therapy.

Treatment

Previous Treatment

Previous to IFX, a total of 141 patients (61.6%) had received EEN, 191 (83.4%) had been treated with steroids, and 71 patients (31%) with 5-aminosalicylates. Immunomodulating drugs had been prescribed in most patients. A total of 208 patients (90.8%) were treated with thiopurines before stepping-up to IFX and 47 patients (20.5%) were treated with methotrexate. Three patients (1.3%) received adalimumab therapy before IFX was started, respectively for 2, 3, and 12 months. Ten patients (4.4%) underwent bowel surgery before IFX was initiated, 35 patients (15.3%) underwent surgical fistula correction and in 3 cases (1.3%) both were performed. There were no significant differences between the 3 groups (Supplemental Digital Content 2, Table, *http://links.lww.com/MPG/A916*).

Infliximab Treatment

In the majority of patients (n = 222, 97%) IFX was initiated as step-up therapy because conventional therapy failed to induce or maintain remission. IFX was started as initial treatment in 4 patients, of which 1 had perianal fistulizing disease and the other 3 patients started with treatment with IFX as part of a randomized controlled trial (Infliximab Top-Down Study in Kids with Crohn disease [ITSKids] Erasmus Medical Centre Rotterdam). In 3 patients there were other indications for initiating IFX, namely comorbidity with juvenile idiopathic arthritis in 1 patient, erythema nodosum in the second and fistulizing disease after laparoscopic appendectomy in the third. Median duration of IFX treatment was 25 months (IQR 13–43.7). The median time from the start of IFX therapy to the end of the observation period was 32 months (IQR 18.3–53.9). In general, patients received a 3-dose induction scheme with infusions at 0, 2, and 6 weeks followed by scheduled IFX maintenance therapy at 5 mg/kg every 8 weeks. In 18 patients (7.9%) IFX has been temporarily discontinued for a median of 7.0 months (IQR 4–12). IFX was restarted in all these patients using the induction scheme as previously described. In 8 of 18 patients (47.1%), IFX was stopped after induction because remission of refractory disease (n = 5) or healing of perianal fistulas (n = 3) was achieved. Eventually, 48 patients (21%) experienced LOR and needed either surgery or switch to other medical therapy (see Loss of Response to Infliximab).

Efficacy

Antibodies to Infliximab

Antibodies were measured in case of clinical suspicion of relapse (Fig. 1). A total of 162 patients (70.7%) were tested for antibodies to IFX, 25 of 162 patients (15.4%) were antibody positive at a median of 14 months (IQR 5.9–26) after therapy initiation. The median level of ATIs at first positive titre measurement was 63 AU/mL (IQR 25–430). IFX therapy was stopped in 20 of 25 patients with ATIs, in most cases because ATI formation was accompanied by LOR (n = 16). Positive ATIs were accompanied by undetectable IFX trough levels in all patients except 1, in which ATI titre was 30.0 AU/mL and IFX drug level was adequate (4.00 mg/L).

Immunomodulator Use and Antibodies to Infliximab Formation

Six out of 62 patients in the CCI group developed ATIs (10%), 11 of 81 in the ECI group (14%), and 8 of 19 in the IFX group (42%). Kaplan-Meier analysis comparing the incidence of ATI formation showed significantly higher probability of developing ATIs in patients in the IFX monotherapy group compared with those in the CCI ($P = 0.003$) and the ECI group ($P = 0.008$), log-rank overall 0.002 (Fig. 2). The incidence of ATI was similar in the CCI and ECI group. In the ECI group, all 11 positive ATI patients developed ATIs in the IFX monotherapy period as immunomodulatory therapy had been stopped at least 4 months before positive titres were measured. Furthermore, 55 patients in this group received concomitant immunomodulators for a duration of <12 months (median 5 months, IQR 3–6.7); 10 of these patients (18.2%) developed ATIs. Among the 26 patients receiving concomitant immunomodulators for more than 12 months (median

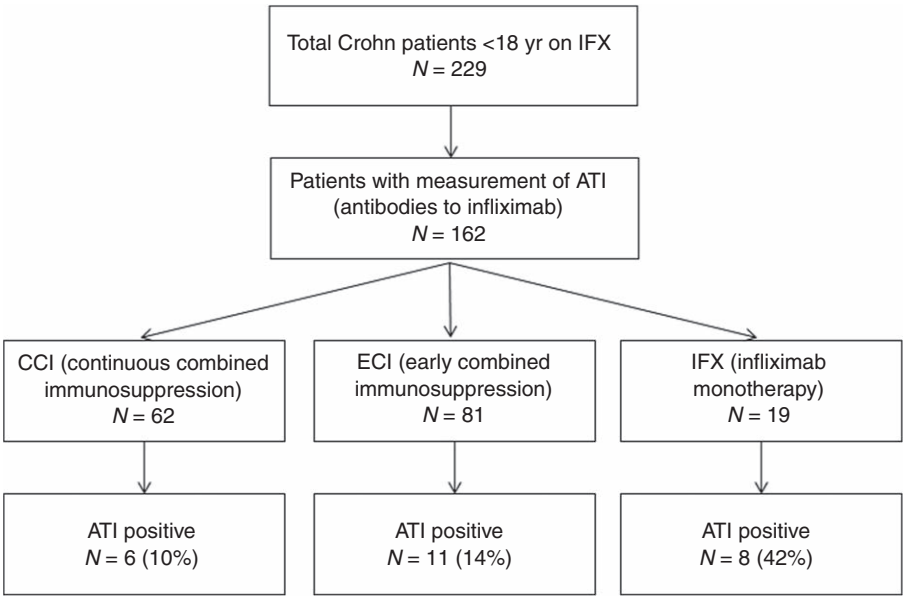

FIGURE 1. Patient flow chart showing the patients included and the different treatment groups. ATI = antibodies to infliximab; IFX = infliximab.

20.6 months, IQR 15–37), 1 positive ATI titre was found (3.8%). This patient was on combination therapy for 23 months and developed antibodies after 27 months of monotherapy with IFX (Fig. 2).

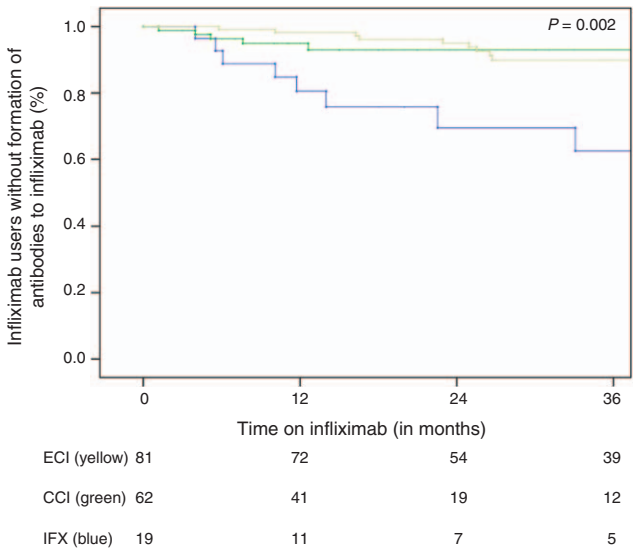

FIGURE 2. Kaplan-Meier plot demonstrating the percentage of infliximab users who did not develop antibodies to infliximab. Children with continuous combined immunosuppression (CCI, green lline) are compared with those on early combined immunosuppression (ECI, yellow line) and those on infliximab monotherapy (IFX, blue line). Event is defined as formation of positive antibodies (>12 AU/mL), censor is defined as discontinuation of infliximab or end of observation period. The numbers on the lowest 3 lines indicate the number of patients being represented at that point in time. The *P* value was calculated by the log-rank test. CCI = continuous combined immunosuppression; ECI = early combined immunosuppression; IFX = infliximab.

Description of Immunomodulatory Use

One hundred eighteen patients (66.7%) received thiopurines, including azathioprine (n = 115) and mercaptopurine (n = 3). All patients had started using immunomodulating drugs before initiation of IFX. In 15 out of these 118 patients (12.7%), positive ATI titres were found. Six of 15 patients developing ATIs received immunomodulatory therapy at time of ATI formation, whereas the remaining 9 patients were part of the ECI group in which thiopurines were already stopped as previously described. There were 25 patients (15.4%) treated with methotrexate in whom 2 patients (0.08%) developed ATIs.

Antibodies to Infliximab–free Survival Rates

Kaplan-Meier estimates of the probability of remaining ATI free at 12, 24, and 36 months after introduction of IFX in the CCI group were 93.4% (confidence interval [CI] 87.1–99.7), 91% (CI 83.4–98.6), and 91% (CI 83.4–98.6), respectively. In the ECI group respectively 97.5% (CI 94–101), 93% (CI 87.1–98.9), and 85.6% (CI 76.8–94.4) and in the IFX group respectively 72.6% (CI 52–93.2), 57.7% (CI 33–82.4), and 48.1% (CI 21.3–75) (Fig. 3).

Treatment Escalation of Infliximab

In 123 of all patients (53.7%) treatment escalation was performed by shortening the dose interval (n = 63), increasing the dosage (n = 13), or both (n = 47). The need for treatment escalation was not different between the groups, with respectively 40 out of 86 patients (46.5%) in CCI, 65 out of 115 (56.5%) in ECI, and 18 out of 28 (64.3%) in the IFX group. Treatment escalation took place in 14 of 25 patients developing ATIs. In the majority of these patients (10 out of 14), treatment escalation was performed before ATI development, at a median of 19.8 months (IQR 1.6–39.3) before positive titres were measured. This included shortening the interval in 5 patients at a median of 19.1 weeks (IQR 3–23.9) before ATIs, dose escalation up to 10 mg/kg in 2 patients at either

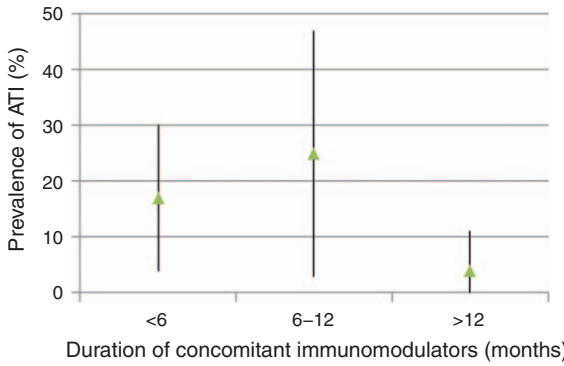

FIGURE 3. Prevalence of ATI in early combined immunosuppression group. ATI = antibody to infliximab.

3 days or 24.5 months and finally both interval and dose escalation in the remaining 3 patients at 7.7 weeks, 40 months, and 64 months before ATIs. Four of 14 patients had dose escalation up to 10 mg/kg at a median of 6 weeks (IQR 4.2–11.4) after positive ATI titres were found. Three of these 4 patients remained in clinical remission (Paediatric Crohn's Disease Activity Index score 0) with continuing IFX therapy, although IFX trough levels were low in 1 patient (in the other 2 patients IFX levels were not measured). The other patients switched to adalimumab 5 months after dose escalation as IFX through levels remained low. Treatment escalation was not attempted in 11 of 25 patients developing ATIs, as either adalimumab (n = 5) or certolizumab (n = 1) therapy was initiated immediately after ATI formation, an allergic reaction occurred (n = 4) or remission was achieved (n = 1).

Loss of Response to Infliximab

During follow-up, 48 patients (21%) experienced LOR after a median of 15.5 months (IQR 7.5–33.2). In 32 patients IFX dose escalation was performed before LOR. In 16 patients neither dose escalation nor shortening of interval was performed. As a consequence, 28 patients switched to adalimumab therapy and 1 patient to certolizumab, and 19 underwent bowel surgery. Sixteen out of 25 patients (64%) with ATIs had LOR, compared with 32 of 137 patients (19%) without ATIs ($P < 0.00002$, log rank 0.02). ATI titres were measured in 36 of 48 patients (75%). Fourteen of 62 patients (23%) in the CCI group lost response to IFX therapy and in 3 patients ATIs were positive. Out of 81 patients in the ECI group, 14 patients (17%) had LOR and 8 of 14 patients were ATI positive. Finally, 8 of 19 patients (42%) in the IFX group developed LOR and in 5 of them ATIs were found.

Safety

During the observation period of IFX treatment of the entire cohort a total of 134 adverse events were reported in 97 patients (42.4%), including infusion reactions in 10 patients (4%). Three out of 10 patients had positive ATI titres and low IFX levels at time of the infusion reaction. In 2 patients this was the first time positive ATIs were measured, whereas in the other patient first detection of ATIs was 9 months earlier. In all but 1 patient developing allergic reactions IFX therapy was ceased. Other adverse events noted were skin eruptions (64 patients, 28%) and infections, which required oral or topical antibiotics (38 patients, 17%). One patient developed pancytopenia with several infections during induction requiring temporal discontinuation of IFX for 1 month, after which therapy could be safely reinitiated. IFX was permanently stopped in 72 patients (31.4%) after a median of 17 months (IQR 10.1–36.7), because of LOR (n = 30, 13.1%), positive ATIs (n = 17, 7.4%), remission (n = 14, 6.1%), preference of the patient for adalimumab (n = 1), or adverse events (n = 10, 4.4%). After discontinuation of IFX treatment, most patients switched to adalimumab therapy (n = 42, 18.3%). In others, surgery was performed (n = 11, 4.8%) or watchful waiting policy was initiated (n = 19, 8.3%), usually with thiopurine monotherapy (n = 14, 6.1%).

DISCUSSION

This observational study shows that in children with CD, IFX treatment with concomitant immunomodulator use is associated with a significant reduction of ATI formation and LOR. There was no significant difference in ATI formation between patients on continuous and ECI. Our findings imply that the immune response to IFX is at its strongest in the first year of exposure to IFX.

ATI formation was detected in 15% of the total cohort. This proportion is smaller than reported in 3 previous small paediatric studies (14,20,21), which showed ATI formation in about a third of patients with CD, and similar to ATI prevalence in adults with CD on IFX maintenance therapy (7%–12%) (13,22). Our conclusion that combination therapy reduces ATI formation and LOR is in accordance with the conclusions of Dulai et al (23). In a systematic review the effect of combination therapy on clinical remission, mucosal healing, and pharmacokinetics was evaluated in adult inflammatory disease. The conclusion was that comedication of immunomodulator and antitumour necrosis factor therapy prevents antibody formation and improves treatment efficacy in CD. Furthermore, the ACCENT I trial also showed a trend towards less ATI and higher clinical response rates in patients receiving concurrent immunomodulation during IFX therapy (24). Another randomized trial in adults showed combination therapy to be associated with higher median IFX trough and decreased C-reactive protein levels compared to IFX monotherapy (19). High incidence of LOR in patients who develop ATI is reported in a recent meta-analysis involving 10 studies and 668 patients, showing patients with ATI to have a threefold risk of LOR to therapy (11). Recent data of 502 children with CD show an increase in IFX response durability in patients treated with concomitant immunomodulator for more than 6 months (25).

Concerns about the lymphoproliferative risk of long-term use of thiopurines may urge paediatric gastroenterologists to shorten the period of thiopurine use. The findings of our cohort study suggest that discontinuation of immunomodulators after initial combination therapy may also be a reasonable strategy. Lymphoma risk seems to reduce after discontinuation of immunomodulating therapy (26). We observed a lower prevalence of ATI formation in children on combination therapy for at least 12 months, but the analysis lacked power. The optimal duration of combination therapy before moving to IFX monotherapy remains to be prospectively investigated.

The benefit of combination therapy (reduction of ATI formation) relative to IFX monotherapy should outweigh the risk of serious infections and malignancies to achieve an optimal treatment strategy for paediatric CD.

A recent study constructed a Markov model to assess age-specific risks and benefits of combination therapy compared to IFX monotherapy. They found combination therapy to be the preferred option that outweighed the risks for most patients with CD younger than 65 years (26). Young men with limited disease extent may be an exception due to the increased risk of developing hepatosplenic T-cell lymphoma. Although the use of an immunomodulator in combination with IFX is associated with less ATI formation, uncertainty remains on the optimal duration of combination therapy in the face of lymphoma risk.

Limitations of the present study were the retrospective nature, because measuring ATI and IFX trough levels were not determined by protocol. As a result, actual antibody development will be underestimated because not in all patients antibodies were assessed. We also observed a time trend with more frequent assessment of ATI and IFX levels in later years of the observation period. Furthermore, the physicians' decision to determine ATI and to escalate or discontinue IFX treatment was not protocol based, but merely triggered by the appearance of gastrointestinal symptoms. As a consequence, the group of patients exposed to ATI measurement and dose escalation possibly included patients with symptoms of either irritable bowel syndrome or infection. As not all patients were treated in a uniform manner, the generalizability of our results may be affected. Finally, selection bias may have occurred because only two third of the centres in the Netherlands treating patients with CD participated in the present study. All centres, however, adhere to the same national guideline for the treatment of paediatric CD and we therefore consider the risk of bias to be small. To our knowledge this observational study in 229 patients is the first to evaluate the influence of concomitant immunomodulator use on ATI formation and LOR in paediatric patients with CD. Strong point of the present study is the real-life setting with a broad spectrum of patients with CD.

CONCLUSIONS

In summary, the findings of this observational study question the efficacy of IFX monotherapy from the start and show that concomitant immunomodulator use in paediatric patients significantly reduces antibody formation and risk of LOR. Combination therapy for approximately 12 months from initiation of IFX, followed by IFX monotherapy, may be an equally effective alternative to continuous combination therapy. These data highlight the need to further examine the effect of cessation of immunomodulatory therapy on ATI development and long-term remission in children with CD treated with IFX.

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