Monotherapy With Infliximab Versus Combination Therapy in the Maintenance of Clinical Remission in Children With Moderate to Severe Crohn Disease

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ABSTRACT

Objectives: The aim of the present study was to compare the efficacy and safety of 2 protocols of maintenance therapy with infliximab (IFX) and an immunomodulatory agent in pediatric patients with Crohn disease (CD): withdrawal of immunomodulators versus continuation of immunosuppressants.

Methods: The present multicenter randomized open-label trial included 99 patients with CD (ages 14.5 ± 2.6 years) who were administered IFX (5 mg/kg body weight) along with an immunomodulatory agent (azathioprine 1.5–3 mg/kg body weight per day, methotrexate 10–25 mg/week). After 10 weeks of the induction therapy, 84 responders were centrally randomized into 1 of the following groups: group I (n = 45) in which IFX and an immunomodulatory agent were continued up to week 54 and group II (n = 39) in which the immunomodulatory agent was discontinued after 26 weeks.

Results: The induction therapy was reflected by a significant decrease in Pediatric Crohn's Disease Activity Index (PCDAI) and Simplified Endoscopic Activity Score for Crohn's Disease (SES-CD) values. After the maintenance phase, the analyzed groups did not differ significantly in terms of the clinical response loss rates and final PCDAI and SES-CD scores. Furthermore, no significant intragroup differences were documented between mean PCDAI scores determined at the end of induction and maintenance phases. Intensification/modification of the treatment was required in 13 of 45 (29%) and 11 of 39 (28%) patients of groups I and II, respectively. A total of 9 serious adverse events were documented; none of the patients died during the trial.

Conclusions: Twenty-six weeks likely represent the safe duration of combined IFX/immunomodulatory therapy in our sample of pediatric patients with CD.

Key Words: children, Crohn disease, infliximab

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Crohn disease (CD) is an inflammatory condition of unknown etiology, which is classified in the inflammatory bowel disease group along with ulcerative colitis (1,2). Thus far, no consensus on an effective pediatric CD treatment protocol has been developed (3). There is a reasonable consensus based on randomized controlled trials indeed, but in adult patients, not in children. Consequently, the goals of both the pharmacotherapy and surgical management are limited to obtaining the longest possible remission and preventing relapse (4,5).

In recent years, monoclonal antibodies against tumor necrosis factor-α, infliximab (IFX) and adalimumab (ADA), are gaining increasing popularity in CD management (6,7). IFX was approved for the treatment of acute CD in pediatric patients who do not respond to conventional therapy, and in those in whom CD is associated with fistulization (8,9). Both the clinical trials (10,11) and meta-analyses (12–14) confirmed high efficacy of IFX with regards to the induction and maintenance of remission. The data on the efficacy and safety of combined therapy with IFX and immunomodulatory agents, however, are inconclusive. Although the results of several studies suggest that the efficacy of the combined therapy is higher than in the case of IFX alone (15–18), there are many concerns related to the potential risk of adverse events (AEs) associated with such an approach, particularly a higher incidence of lymphatic system malignancies and severe infections in patients receiving concomitant immunomodulatory and biological therapy (19,20). Furthermore, the question when the immunosuppressive therapy should be discontinued to avoid severe complications in pediatric patients has not been addressed to date. In our study, the immunomodulatory agent was withdrawn starting from week 26. The decision on the duration of the follow-up was based on a study

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by Van Assche et al (21), who showed that there may be no additional benefit with continuation of immunosupressants beyond 6 months, although the risk of AEs is higher.

The aim of the present multicenter randomized trial was to compare the efficacy and safety of 2 protocols of maintenance therapy with IFX and an immunomodulatory agent in pediatric patients with CD: withdrawal of immunomodulators and continuation of immunosupressants. The secondary objective of the study was to confirm the efficacy of IFX in achieving remission in this group of patients. To the best of our knowledge, the present study is the first one involving such a large group of pediatric patients, performed to analyze the effects of immunomodulatory therapy discontinuation.

METHODS

Patients

The Concomitant Immunomodulator for Maintenance Infliximab Therapy study included 7- to 17-year-old patients in whom the diagnosis of CD was confirmed by endoscopy and biopsy. The differential diagnoses included infectious (eg, *C difficile*) and allergic colitis, which have been ruled out in our patients. All of the participants had a history of moderate to severely active CD, as defined by Pediatric Crohn's Disease Activity Index (PCDAI) values >30 points (22), and lacked or lost the response to previously given pharmacotherapy other than biological therapy. The endoscopic activity of CD was scored with the Simplified Endoscopic Activity Score for Crohn's Disease (SES-CD) at weeks 0, 10, and 54. SES-CD is a simple, reproducible, and easy-to-use endoscopic scoring system for patients with CD based on the following 4 variables, each scored between 0 and 3 points: ulcer size, ulcerated surface, affected surface, and stenosis determined in 5 ileocolonic segments (23).

The presence of active fistula was not the exclusion criterion from the trial. Permitted concomitant treatments included all of the therapies approved by the doctor in charge of the patient taking part in the trial. Patients were ineligible if they had received any biological agent within 8 weeks before or during the trial.

All of the procedures were reviewed and approved by the independent review board. The patients and their caregivers gave their written informed consent before the start of any procedure.

Study Design

The study was designed as a multicenter randomized open-label trial (registration number NCT01559142). It involved 15 Polish pediatric gastroenterology centers (all of the academic tertiary institutions), and thus the hereby reported findings are likely generalizable for the other patient populations. During screening phase, the results of laboratory tests (days 14–0) and endoscopic examination (up to 3 months before day 0) were obtained to enroll the eligible patients. During the induction phase (weeks 0–10), the remission of CD was induced with 3 doses of IFX (5 mg/kg body weight [b.w.]) given at weeks 0, 2, and 6. Simultaneously, steroid therapy was withdrawn in patients who had received such a treatment previously. In accordance with the protocol, the dose of steroids was decreased gradually (5 mg/week), up to complete withdrawal in week 2. Reimplementation of steroids, however, was considered to be an option of rescue therapy. On week 10, the therapeutic responses were evaluated on the basis of PCDAI score and endoscopic examination. Patients with the clinical response (ie, decrease in PCDAI ≥15 points and ≤30 points) were centrally randomized into 1 of the following maintenance protocols: IFX with an immunomodulatory agent (azathioprine [AZA] 1.5–3 mg/kg b.w. per day or methotrexate 10–25 mg/week; group I) or IFX with the immunomodulatory agent discontinued after 26 weeks of treatment (group II). Randomization list was prepared for 100 patients in groups of 10. A total of 100 randomization envelopes were prepared with subsequent numbers. Central off-site randomization service by envelope system provided treatment allocation. Because both AZA and methotrexate have been introduced before the beginning of the study, their doses were stable and maintained during the trial.

During the maintenance phase (weeks 10–54), the infusions of IFX (5 mg/kg b.w.) were given every 8 weeks, and the follow-up visits were scheduled at weeks 14, 22, 30, 38, and 46 for both groups. At week 26, the immunomodulatory agent was discontinued in patients from group II. The duration of concomitant therapy has been tempered by data from a study that showed that there may be no additional benefit with continuation of immunosupressants beyond 6 months of combination therapy (21).

The therapeutic response was evaluated at week 54 based on PCDAI score and endoscopic examination, and the patients were assessed for the presence of any potential serious AEs (sAE). The flowchart illustrating the course of the study is presented in Figure 1.

Concomitant Medications

Steroid therapy administered before the enrollment was withdrawn up to week 2 of the induction phase. Before that, in accordance with the protocol, the dose of steroids was gradually decreased. Any reimplementation of steroids was considered to be a secondary endpoint of the maintenance phase. All of the other concomitant therapies, except the biological treatment, were approved if accepted by the doctor in charge.

Efficacy Evaluations

Patients were assessed at baseline and at weeks 10 and 54. Each visit included a physical examination and laboratory tests measuring the levels of inflammatory indicators. Also, body mass index (BMI) was calculated during each visit. Additionally, the clinical activity of the disease was assessed using PCDAI, and the endoscopic activity was scored using SES-CD at weeks 0, 10, and 54.

Safety Evaluations

AEs were monitored throughout the entire study period. Data on all of the study participants were included in the safety analyses. At each visit, AEs were documented and blood samples were obtained for laboratory evaluation. Any withdrawals from the study because of AE or sAE were recorded in the study documentation.

Endpoints

The primary endpoint was the clinical remission defined as PCDAI ≤10 points after 1 year of maintenance therapy. The secondary endpoints included the necessity of intensifying/modifying maintenance therapy, such as surgical treatment, increased dose of the immunomodulatory agent or IFX, and steroid reimplementation.

Statistical Methods

The size of the sample was calculated for the remission maintenance phase. Assuming 0.8 statistical power, 0.05 α

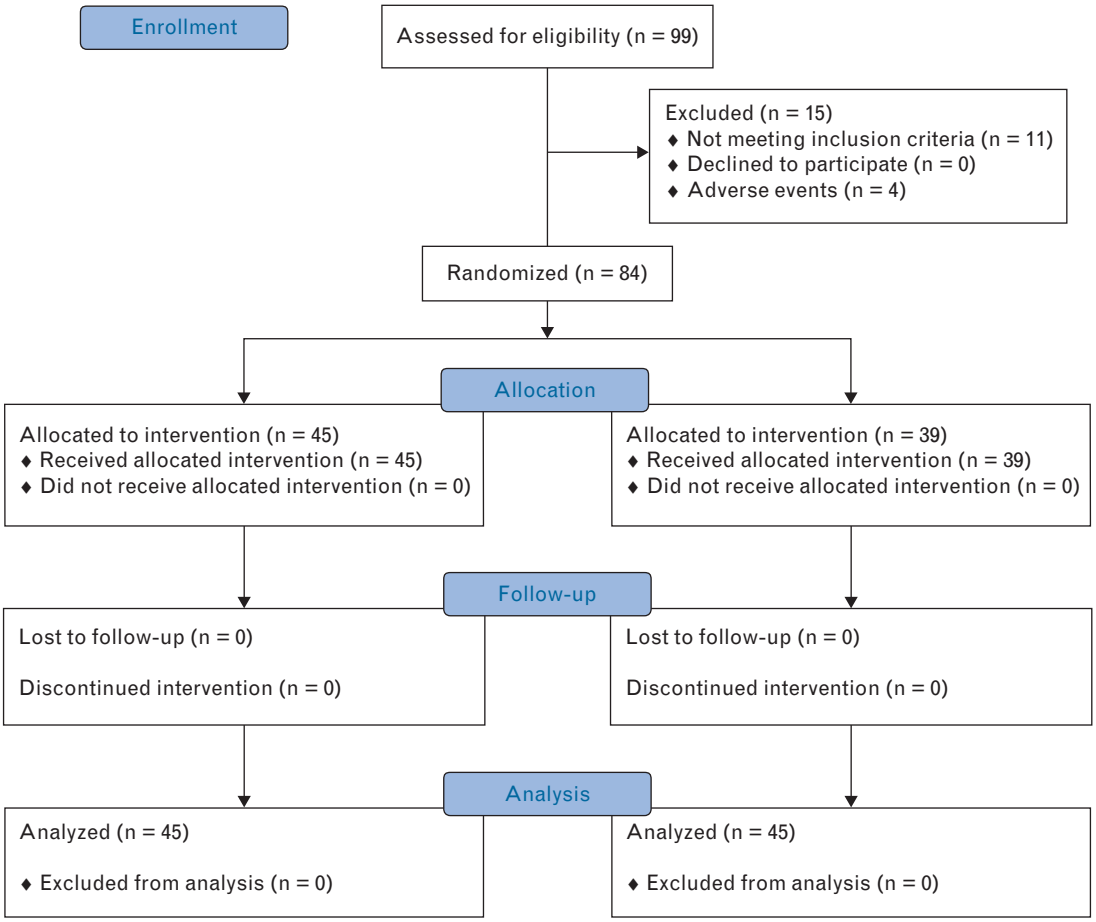

FIGURE 1. Study flow.

coefficient, and 0.3 difference between the prevalence of the endpoint in both groups, the required size of each group was estimated at 39 (78 in total) with the χ^2 test. Assuming 20% of patients lacking responses during the induction phase, the required number of patients for this phase was estimated at 98.

The intention-to-treat analysis of the induction phase outcome included the determination of the fractions of patients with primary and secondary endpoints. During the intention-to-treat analysis of the maintenance phase outcome, the χ^2 test or the Fisher exact test was used to compare the frequencies of primary and secondary endpoints, depending on the expected numbers. The Mann-Whitney *U* test was used for the analysis of intergroup differences in the level of quantitative variables (BMI, hemoglobin concentration, platelet count, C-reactive protein, SES-CD score, and PCDAI score), whereas the intragroup differences in the levels of these variables were analyzed with the Wilcoxon signed-rank test. All of the calculations were conducted with StatsDirect 2.7.9 package (StatsDirect Ltd, Cheshire, UK).

RESULTS

Patients

A total of 99 children (62 boys and 37 girls) ages 14.54 ± 2.61 years, with CD diagnosed at the mean age 12.55 ± 1.93 years, were enrolled in the induction phase. A total of 15 of them, however, were excluded because they did not reach the clinical response (n = 11) or experienced AEs (n = 4) during the induction treatment. Therefore, 84 patients with the clinical response/remission were eventually qualified to the maintenance phase and centrally randomized into 1 of the following groups: IFX with an immunomodulatory agent (group I; n = 45) and IFX with the immunomodulatory agent discontinued after 26 weeks of treatment (group II; n = 39). All of the patients completed the study. The demographics and clinical characteristics of the analyzed patients at day 1 of the induction phase are presented in Table 1.

Efficacy

As a result of induction therapy, the clinical response, defined as 15 points decrease in PCDAI and PCDAI <30, was obtained in 84 of 99 patients, including 55 of 84 (65.5%) patients with clinical remission defined as PCDAI ≤10. The subset of patients with remission included 30 of 45 (66.7%) and 25 of 39 (64.1%) individuals from groups I and II, respectively; this difference turned out to be insignificant on statistical analysis. Mean PCDAI score at baseline was 48.10 points (median 51, interquartile range [IQR] 35–55) compared with 12.50 (median 10, IQR 5–17.5) after completing the induction phase at week 10; this difference proved statistically significant ($P < 0.05$; Fig. 2A). Moreover, there was a significant decrease in SES-CD score; the mean scores at baseline and after the induction phase were 16.62 points (median

TABLE 1. Demographic and clinical characteristics of study participants at day 1

Variable	Group I (n = 45)	Group II (n = 39)	P
Age, y	14.4 ± 2.28	15.1 ± 2.17	0.152
Duration of CD, y*	1.38 (0.54–2.63)	1.10 (0.48–2.77)	0.971
PCDAI score	49.22 ± 13.28	45.53 ± 11.52	0.344
SES-CD	18.60 ± 11.19	13.74 ± 8.62	0.063
CRP, mg/dL	3.33 (1.0–22.0)	2.20 (1.08–22.8)	0.875
ESR, mm/h	36 (28–55)	28 (15–52)	0.060
Hemoglobin, mg/dL	11.6 (10.5–12.3)	12.0 (10.9–13.0)	0.195
BMI, kg/m^2	16.8 (15.2–19.6)	17.3 (16.3–20.4)	0.238

Values presented as mean ± standard deviation, median (interquartile range). BMI = body mass index; CD = Crohn disease; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; PCDAI = Pediatric Crohn's Disease Activity Index; SES-CD = Simplified Endoscopic Activity Score for Crohn's Disease.

*Defined as the period between the onset of CD and the first administration of the study medication.

15, IQR 9–24) and 5.22 points (median 3, IQR 0–8), respectively ($P < 0.05$; Fig. 2B). The 2 groups randomized for the maintenance phase did not differ significantly after the induction period; PCDAI scores determined at the end of this phase (tenth week) were 12.38 and 9.36 in groups I and II, respectively.

A subset of patients with perianal fistulae (n = 25) was enrolled in the induction phase. A total of 21 of 25 (84%) individuals from this subgroup showed clinical response at week 10, including 16 of 21 (76.2%) patients with remission; fistula closure was found in 16 of 25 (64%) patients who completed the induction phase.

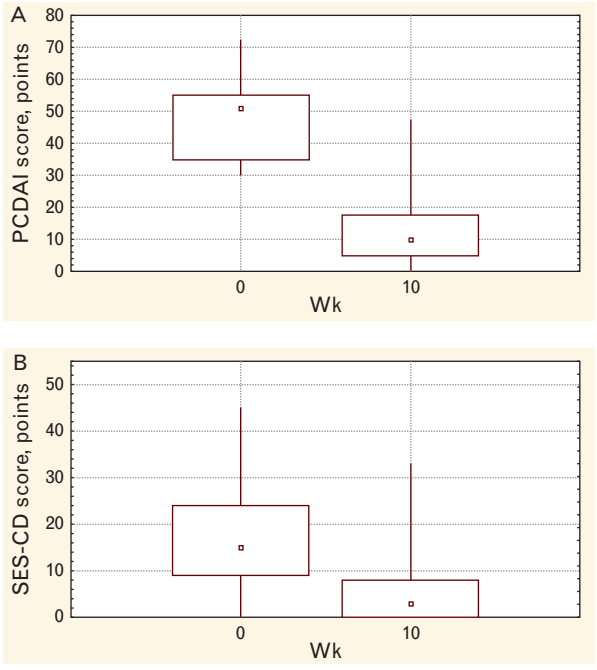

FIGURE 2. Median of PCDAI (A) and SES-CD (B) scores at randomization and after completing the induction phase. Boxes and whiskers represent interquartile ranges and ranges, respectively. PCDAI = Pediatric Crohn's Disease Activity Index; SES-CD = Simplified Simplified Endoscopic Activity Score for Crohn's Disease.

After the maintenance phase at week 54, the loss of clinical response was documented in 2 of 45 patients from group I (4%) and in 2 of 39 patients from group II (5%). There was no significant intergroup difference in the rate of clinical response loss ($P > 0.05$). Mean PCDAI score of patients who completed the study at week 54 was 8.60 points (median 5, IQR 0–12.5), whereas the mean final SES-CD score amounted to 4.37 (median 0, IQR 0–6). In group I, mean PCDAI and SES-CD scores determined at week 54 amounted to 8.48 points (median 5, IQR 0–15) and 5.56 points (median 1, IQR 0–9), respectively, whereas the mean PCDAI and SES-CD scores in group II were 8.31 points (median 5, IQR 0–10) and 3.82 points (median 3, IQR 0–6), respectively. Statistical analysis revealed that groups I and II did not differ significantly in terms of final PCDAI and SES-CD scores at week 54, also when only individuals being at remission at week 10 were compared (not shown).

Furthermore, no significant differences were documented between mean PCDAI and SES-CS scores determined at the end of induction (10th week) and maintenance (54th week) phases in both group I (12.38 vs 8.48 points and 4.69 vs 5.33, respectively) and group II (9.36 vs 8.31 and 5.56 vs 3.88, respectively). Intensification/modification of the treatment was required in 13 of 45 (29%) and 11 of 39 (28%) patients of groups I and II, respectively; this difference did not prove statistically significant. Steroids needed to be reimplemented in 3 of 45 (6.7%) and 3 of 39 (7.7%) patients of groups I and II, respectively; also, the intergroup difference in the fraction of the patients who were reimplemented steroids did not turn out to be significant on statistical analysis. Other intensification/modification options included surgery (4/45 in group I vs 1/39 in group II), IFX dose escalation (1/45 vs 1/39), and intensification of IFX dosage regimen (7/45 vs 7/39). Compared with baseline, 84 patients who completed the study showed an increase in BMI and hemoglobin concentration and a decrease in C-reactive protein level (Table 2).

Safety

IFX proved to be safe and well tolerated. A total of 9 sAEs were documented in 99 enrolled patients. Four sAEs were observed in 4 patients during the induction phase: generalized urticaria, systemic allergic reaction, chickenpox, and cervical lymphadenopathy associated with the activation of Epstein-Barr virus (EBV) infection. All of these sAEs necessitated the withdrawal from the trial during the induction phase. Another 5 sAEs were documented in 5 patients who were subjected to the maintenance therapy; these included activation of EBV infection (n = 3), psoriatic lesions of the scalp (n = 1), and diarrhea (n = 1). Additionally, 3 opportunistic

TABLE 2. Median (interquartile ranges) BMI, and hemoglobin and CRP concentrations determined at weeks 10 and 54

Phase	Group I (n = 45)	Group II (n = 39)	P
BMI, kg/m^2			
Week 10	18.4 (16.9–20.7)	19.2 (17.7–21.2)	0.144
Week 54	18.6 (17.2–21.9)	19.8 (18.4–22)	0.288
Hemoglobin, mg/dL			
Week 10	12.3 (11.6–13)	12.5 (11.3–13.5)	0.728
Week 54	12.8 (12.1–13.6)	12.8 (11.9–13.7)	0.810
CRP, mg/dL			
Week 10	1.24 (0.16–3.87)	0.80 (0.12–3.3)	0.406
Week 54	0.88 (0.1–3.8)	0.49 (0.1–5)	0.971

BMI = body mass index; CRP = C-reactive protein.

infections, EBV, herpes simplex virus, and chickenpox, were noted throughout the study period. None of the patients died during the trial. The detailed profile of AEs is presented in Table 3.

DISCUSSION

The aim of the present study was to compare the efficacy and safety of 2 protocols of maintenance therapy with IFX and an immunomodulatory agent in pediatric patients with CD: withdrawal of immunomodulators and nonwithdrawal of immunosupressants, both implemented following the induction of remission with 3 IFX infusions. The study showed that the 2 protocols of maintenance therapy did not differ significantly in terms of their efficacy, defined as the clinical response loss rates and final PCDAI and SES-CD scores; IFX was safe and well tolerated by pediatric patients with CD; and 26 weeks likely represented the safe duration of combined IFX/immunomodulatory therapy in this group.

Literature data dealing with the problem in question are sparse. The results of previous studies, involving mostly adult patients (24–26), suggest that biological agents are more efficient in inducting a remission of active CD (27), in preventing an exacerbation (28), and in patients who neither respond nor tolerate immunosuppressive agents (4) and in those with fistulae (29).

The REACH project is the principal study confirming the efficacy of IFX in pediatric patients, and is referred to by all of the other authors. The present large prospective multicenter study involving 112 children with moderately severe and severe CD showed 88.4% clinical response rate and 58.9% remission rate after 10 weeks of treatment (10). Our group also has positive experiences with biological therapy of children with CD (30). In our previous study analyzing the influence of IFX on the healing of intestinal mucosa and clinical remission in patients with severe CD, remission and clinical response were achieved in 33% and 39% of studied children, respectively. Moreover, complete mucosal healing was observed in 22.7% of the patients. We achieved similarly positive results during the maintenance therapy with IFX (30). Pediatric anti–tumor necrosis factor trial, the IMAgINE 1 study, evaluated the safety and efficacy of ADA double-blind maintenance dosing regimens following open-label induction for pediatric patients with moderate to severe CD. ADA induced and maintained clinical remission of children with CD with a safety profile comparable to that of adult patients with CD. In the present study, more children who received high than low dose were in remission at week 26, but the difference between dose groups was not statistically significant (31).

There is no published pediatric research based on similar methodology, that is, using the protocol in which the immunomodulatory treatment was withdrawn (as in the 26th week of combined therapy in our study) for the purpose of comparative analysis of studied protocols in terms of their efficacy and safety. The principal trial we refer to is SONIC, the large, blind randomized trial comparing the efficacy and safety of IFX or AZA used in monotherapy with the analogous indicators of combined therapy with these agents in 508 adult patients with CD (15). Patients receiving the combined therapy had a higher rate of clinical remissions not requiring steroid therapy as compared with those receiving monotherapy with either agent, whereas the safety profiles of all of the protocols were similar (15).

Our findings are consistent with the above-mentioned data. After completing the maintenance therapy at week 54, the rate of remission in patients given the combined therapy was similar as in those receiving IFX monotherapy; also, the fraction and profile of AEs documented in both groups were similar. These values were comparable and no statistically significant differences were documented on statistical analysis.

The secondary endpoint of our study pertained to the necessity of intensifying/modifying the maintenance therapy (ie, implementation of surgical treatment, increased dosage of IFX/immunosuppressive agent, or steroid therapy). Also in the case of this endpoint, no significant intergroup differences were documented. The immunomodulatory agent was withdrawn starting from week 26, because we assumed that after 6 months of immunomodulatory therapy the outcome of IFX monotherapy and combined therapy should be comparable, whereas the higher risk of AEs, including the induction of malignancies, remains a concern under investigation (16,17). Previous studies revealed an increased risk of opportunistic infections (31) and hepatosplenic T-cell lymphoma (21,32,33), especially during a longer duration of therapy. Moreover, a study by Van Assche et al (21) showed that there may be no additional benefit with continuation of immunosupressants beyond 6 months of combination therapy. Because of the specific characteristics of our group, involving solely children, the safety profile of the implemented therapy was of vital importance, particularly in view of the fact that the duration of immunosuppression associated with the risk of lymphatic malignancies is unknown (20). Because of longer overall duration of the disease and its treatment, the time of exposure to immunosuppression, the principal risk factor of carcinogenesis, is also prolonged. This definitely requires a longer follow-up with regular control visits and the cooperation with specialists of internal medicine.

The randomized, placebo-controlled trial, GETAID, analyzed the efficacy of IFX combined with AZA in steroid-dependent patients with CD. Patients subjected to the combined treatment were characterized by nearly 2-fold higher remission rate and reduced consumption of steroids, whereas the safety profile was similar to that of the controls (17). The remission rate of our patients was 58.25%. Direct comparisons of these 2 studies, however, would not be accurate because of the different characteristics of patients in GETAID. Our study analyzed steroid-independent pediatric patients, among them 40 individuals who were given steroid therapy at the onset of the experiment.

The novel character of our study constitutes one of its key assets. This is the first relatively large trial addressing the efficacy, safety, and optimal duration of combined therapy with IFX and an immunosuppressant in pediatric patients with CD. We, however, are also well aware of potential limitations of our research, primarily the limited duration of the follow-up period. Also, methodological limitations to the study should be mentioned, namely lack of blinding that may result in selection and performance biases and, eventually, invalidate the results. Nevertheless, we believe that our findings allow for initial conclusions and constitute the basis for further research. Relevant literature lacks unambiguous recommendations regarding the duration of combined biological/immunomodulatory therapy. Furthermore, the evidence on the long-term safety of such a therapeutic approach is not sufficient. Therefore, although

TABLE 3. Adverse events recorded throughout the study

Adverse event	Group I (n = 45)	Group II (n = 39)
Overall (%)	4 (8.9)	5 (12.8)
Systemic urticaria (%)	1 (2.2)	0
Systemic anaphylactic reaction (%)	1 (2.2)	0
Chickenpox (%)	1 (2.2)	0
Activation of EBV infection (%)	1 (2.2)	3 (7.7)
Psoriatic lesions (%)	0	1 (2.6)
Diarrhea (%)	0	1 (2.6)

EBV = Epstein-Barr virus.

26 weeks represented the safe duration of combined IFX/immunomodulatory therapy in our sample, further studies with a longer follow-up period are needed to confirm these preliminary findings.

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