Adalimumab vs Infliximab in Pediatric Patients With Crohn's Disease: A Propensity Score Analysis and Predictors of Treatment Escalation

Jiri Bronsky, MD, PhD[1], Ivana Copova, MD[1], Denis Kazeka, MD[1], Tereza Lerchova, MD, PhD[1], Katarina Mitrova, MD, PhD[1,2], Kristyna Pospisilova, MD[1], Miroslava Sulovcova, MD[1], Kristyna Zarubova, MD[1] and Ondrej Hradsky, MD, PhD[1]

INTRODUCTION: **Two antitumor necrosis factor therapies (infliximab [IFX] and adalimumab [ADA]) have been approved for the treatment of pediatric Crohn's disease (CD) but have not been compared in head-to-head trials. The aim of this study was to compare the efficacy and safety of ADA and IFX by propensity score matching in a prospective cohort of pediatric patients with luminal CD and at least a 24-month follow-up.**

METHODS: **Among 100 patients, 75 met the inclusion criteria, and 62 were matched by propensity score. We evaluated time to treatment escalation as the primary outcome and primary nonresponse, predictors of treatment escalation and relapse, serious adverse events, pharmacokinetics, and effect of concomitant immunomodulators as secondary outcomes.**

RESULTS: **There was no difference between ADA and IFX in time to treatment escalation (HR = 0.63 [95% CI 0.31–1.28] $P = 0.20$), primary nonresponse ($P = 0.95$), or serious adverse events. The median (interquartile range) trough levels at the primary outcome were 14.05 (10.88–15.40) and 6.15 (2.08–6.58) μg/mL in the ADA and IFX groups, respectively. On a multivariate analysis, the combination of anti-*Saccharomyces cerevisiae* antibody negativity and antineutrophil cytoplasmic antibody positivity was a strong independent predictor of treatment escalation (HR 5.19, [95% CI 2.41–11.18], $P < 0.0001$). The simple endoscopic score for CD, L3 disease phenotype, and use of concomitant immunomodulators for at least the first 6 months revealed a trend toward significance on a univariate analysis.**

DISCUSSION: **Propensity score matching did not reveal substantial differences in efficacy or safety between ADA and IFX. The anti-*S. cerevisiae* antibody negativity and antineutrophil cytoplasmic antibody positivity combination is a strong predictor of treatment escalation.**

INTRODUCTION

To date, 2 anti-tumor necrosis factor (TNF) agents have been approved for the treatment of pediatric Crohn's disease (CD): infliximab (IFX) and adalimumab (ADA). Both agents have been proven to be effective and safe in randomized controlled trials (RCTs) (1,2). However, these RCTs differed in some aspects of methodology. In the REACH trial, only patients who responded to induction IFX therapy were randomized, and in the IMAgINE trial, patients who previously failed on anti-TNF therapy were enrolled. Moreover, cessation of immunomodulator (IMM)

therapy was permitted from week 26. Age at enrollment and disease activity based on the Pediatric Crohn's Disease Activity Index (PCDAI) were similar in both studies. However, no direct head-to-head comparison of both anti-TNF agents has been performed in pediatric or adult patients. Several indirect comparisons, including network meta-analyses, have been published, but these rarely consider pediatric populations (3–9). Owing to the low number of pediatric patients per center, it is difficult to perform RCTs that can demonstrate differences between these drugs. In particular, a noninferiority design would require a high

[1]Gastroenterology and Nutrition Unit, Department of Paediatrics, 2nd Faculty of Medicine, Charles University and University Hospital Motol, Prague, Czech Republic; [2]IBD Clinical and Research Centre, ISCARE, Prague, Czech Republic. **Correspondence:** Jiri Bronsky, MD, PhD. E-mail: jiri.bronsky@gmail.com.

number of patients. Therefore, we aimed to perform a propensity score analysis of our cohorts of prospectively followed up patients.

Study aims

The primary aim of this study was to compare the time to treatment escalation between patients treated with ADA and those treated with IFX. Secondary aims were to evaluate primary nonresponse to anti-TNF, predictors of treatment escalation and relapse, safety, pharmacokinetics (PK), and effect of concomitant IMM treatment.

METHODS

Study design and ethical considerations

This prospective observational cohort study was performed using propensity score matching. The study was approved by the local ethics committee, and all participants and/or parents signed written informed consent.

Study subjects and dosage of anti-TNF

Patients naive to biologic therapy, newly started on anti-TNF treatment between 2013 and 2017 (Motol PIBD cohort), were recruited into the study and prospectively followed up according to the standard protocol reflecting usual clinical practice (see Supplementary Figure 1, http://links.lww.com/CTG/A798). Patients were initiated on an anti-TNF agent based on a detailed discussion between the family and the treating physician. The minimal follow-up period required for evaluation of study outcomes was 24 months. Inclusion and exclusion criteria are listed in Supplementary Digital Content (see Supplementary Table 1, http://links.lww.com/CTG/A799). Patients were initiated on a standard dose of anti-TNF: ADA (Humira) 160-80-40 mg s.c. every other week, followed by 40 mg s.c. every other week, and IFX (Remicade) 5 mg/kg i.v. at weeks 0, 2, and 6 and every 8 weeks. No biosimilars were used in this study. In patients weighing less than 40 kg, the dose of ADA was calculated according to the body surface area. When applicable, a decision on therapy intensification (ADA up to 40 mg weekly and IFX up to 10 mg/kg every 4 weeks) was made by the treating physician, based primarily on clinical and laboratory data, and secondarily on trough levels and anti-drug antibodies (ATI) to the respective anti-TNF (reactive therapeutic drug monitoring [TDM]). No proactive TDM was applied during the study period. All patients, except for 3, received IMM (97% azathioprine [AZA], 3% methotrexate [MTX]) from diagnosis until the start of anti-TNF treatment (Table 1).

Primary outcome

The primary outcome of the study was the time to treatment escalation on anti-TNF therapy evaluated by survival analysis after propensity score matching.

Secondary outcomes

The following secondary outcomes were considered: (i) Proportion of patients with a primary nonresponse to ADA or IFX, (ii) identification of predictors of treatment escalation and relapse, (iii) rate of serious adverse events (SAEs) occurring on-treatment, (iv) PK of both drugs, and (v) effect of concomitant IMM treatment.

Definition of treatment escalation, relapse and primary nonresponse

Treatment escalation was defined as dose escalation or interval shortening due to a lack of drug efficacy (not due to adjustment for body weight) or bowel surgery due to disease activity, development of abscess, perianal or intra-abdominal fistula, change of anti-TNF therapy (due to side effects or ineffectivity), need for reinduction (corticosteroids, exclusive enteral nutrition, or antibiotics), or change of IMM treatment (AZA to MTX or vice versa), not dose adjustment for body weight (see Supplementary Figure 1, http://links.lww.com/CTG/A798). For the purpose of secondary subanalysis, dose escalation or interval shortening due to a lack of drug efficacy (not due to adjustment for body weight) was omitted from the abovementioned definition. This situation was marked as relapse.

Primary nonresponse was defined as the need for treatment change (switch to another anti-TNF therapy, treatment interruption, bowel surgery, or persisting need for induction therapy corticosteroids, exclusive enteral nutrition, antibiotics) until week 14 (12–16) due to clinical symptoms (weighted pediatric Crohn's disease activity index [wPCDAI], fistula, and stricture), laboratory signs of disease activity (erythrocyte sedimentation rate, C-reactive protein [CRP], fecal calprotectin [F-CPT]), endoscopic disease activity, need for bowel surgery, drug intolerance (side effects), or noncompliance.

Clinical and laboratory data

At the onset of anti-TNF therapy, we recorded general patient characteristics, factors that may influence the outcome or allocation of patients to the respective treatment group (ADA and IFX), and factors considered as potential predictors of treatment efficacy (Table 1). The data underlying this article will be shared on reasonable request to the corresponding author.

During follow-up, we prospectively recorded the following every 3 months: body height; weight; wPCDAI; CRP; F-CPT; perianal fistulas; extraintestinal manifestations; SAEs; dose and interval of anti-TNF; need for treatment escalation, cessation, or switch, including the reason; concomitant medication; trough levels and ATI to anti-TNF if applicable; and occurrence of primary and secondary outcomes.

Regarding clinical indication, the following checks were performed: bowel ultrasound, magnetic resonance enterography, or endoscopy. Endoscopy, including biopsies and evaluation of simple endoscopic score for CD (SES-CD), was performed before the decision on anti-TNF treatment and before any major therapeutic decision (e.g., switch to another anti-TNF therapy, bowel surgery, and nonresponse).

Patient allocation and statistical analysis

All data were analyzed using R statistical software (version 3.6.0; www.r-project.org). Continuous variables were described as medians and interquartile ranges (IQRs). Categorical variables were described as absolute frequencies and percentages. Missing data were not imputed. The difference between patients treated with ADA and IFX was assessed using the likelihood ratio test on the odds ratio or 2-sample t test, as appropriate. Propensity score matching was performed using the R package MatchIt (version 3.0.2). The model for propensity matching consisted of the SES-CD, stricturing behavior, penetrating behavior, perianal disease, z score of body mass index, and age at the time of anti-TNF onset. Variables were selected based on the clinical decision, according

Table 1. Characteristics of both study groups before propensity score matching

	ADA (N = 31)	IFX (N = 44)	P value
Basic characteristics			
Age	14.18 (11.64–16.34), NA = 0	14.46 (13.24–16.27), NA = 0	0.36
Sex (male)	21 (0.68), NA = 0	24 (0.55), NA = 0	0.25
Smoking	3 (0.1), NA = 0	1 (0.02), NA = 0	0.16
Ethnicity (White)	29 (0.94), NA = 0	43 (0.98), NA = 0	0.37
Family history of IBD	1 (0.03), NA = 0	8 (0.08), NA = 0	0.03
Concomitant immunopathology	3 (0.1), NA = 0	3 (0.07), NA = 0	0.66
Body height (cm)	162 (136.95–170.75), NA = 0	156.55 (148.88–171.52), NA = 0	0.41
Body height (z score)	−1.49 (−5.56–0.53), NA = 0	−2.12 (−3.94–0.26), NA = 0	0.41
Body weight (kg)	44.3 (28.65–58.5), NA = 0	47.25 (37.12–56.08), NA = 0	0.43
BMI (z score)	−1.77 (−2.58–0.53), NA = 0	−1.34 (−1.97–0.4), NA = 0	0.27
Paris classification			
L1	11 (0.35), NA = 0	10 (0.23), NA = 0	0.23
L2	1 (0.03), NA = 0	4 (0.09), NA = 0	0.3
L3	19 (0.61), NA = 0	30 (0.68), NA = 0	0.54
L4a or L4b	22 (0.71), NA = 0	31 (0.7), NA = 0	0.96
B1	23 (0.74), NA = 0	36 (0.82), NA = 0	0.43
B2	4 (0.13), NA = 0	5 (0.11), NA = 0	0.84
B3	4 (0.13), NA = 0	2 (0.05), NA = 0	0.19
B2+B3	0 (0), NA = 0	1 (0.02), NA = 0	0.3
Perianal disease	7 (0.23), NA = 0	12 (0.27), NA = 0	0.64
Growth impairment	10 (0.33), NA = 1	10 (0.23), NA = 0	0.32
Disease activity and labs			
wPCDAI (points)	22.5 (16.88–40.62), NA = 7	32.5 (16.88–40), NA = 4	0.64
CRP (mg/L)	13.6 (8.35–26.25), NA = 4	17 (4.85–29.85), NA = 1	0.55
F-CPT (μg/g)	1,800 (1,080–2,883), NA = 20	1,000 (801–1,720), NA = 11	0.09
Albumin (g/L)	42.8 (40.2–43.8), NA = 6	41.1 (39.4–43.4), NA = 3	0.32
ESR (mm/hr)	28.5 (20–41.25), NA = 3	30 (18–46.5), NA = 1	0.59
ASCA positivity	23 (0.88), NA = 5	34 (0.81), NA = 2	0.4
pANCA positivity	5 (0.19), NA = 5	6 (0.14), NA = 1	0.57
SES-CD (points)	20 (13–27), NA = 2	18 (11.75–21.5), NA = 4	0.2
Treatment			
Time since dg. to anti-TNF start (yr)	1.04 (0.51–1.61), NA = 0	0.6 (0.17–1.23), NA = 0	0.14
EEN during dg.	21 (0.68), NA = 0	37 (0.84), NA = 0	0.1
CS during dg.	6 (0.19), NA = 0	6 (0.14), NA = 0	0.51
IMM during dg.	29 (0.94), NA = 0	43 (0.98), NA = 0	0.37
EEN during anti-TNF start	5 (0.16), NA = 0	7 (0.16), NA = 0	0.98
CS during anti-TNF start	1 (0.03), NA = 0	2 (0.05), NA = 0	0.77
IMM during anti-TNF start	29 (0.94), NA = 0	38 (0.86), NA = 0	0.31

Values are listed as median and interquartile range or median and fraction (%); NA = number of missing values.
ADA, adalimumab; ASCA, anti-*Saccharomyces cerevisiae* antibodies; BMI, body mass index; CRP, C-reactive protein; CS, corticosteroids; dg., diagnosis; EEN, exclusive enteral nutrition; ESR, erythrocyte sedimentation rate; F-CPT, fecal calprotectin; IBDinflammatory bowel disease; IFX, infliximab; IMM, immunomodulators; pANCA, antineutrophilic antibodies; SES-CD, simple endoscopic score for Crohn's disease; TNF, tumor necrosis factor; wPCDAI, weighted pediatric Crohn's disease activity index.
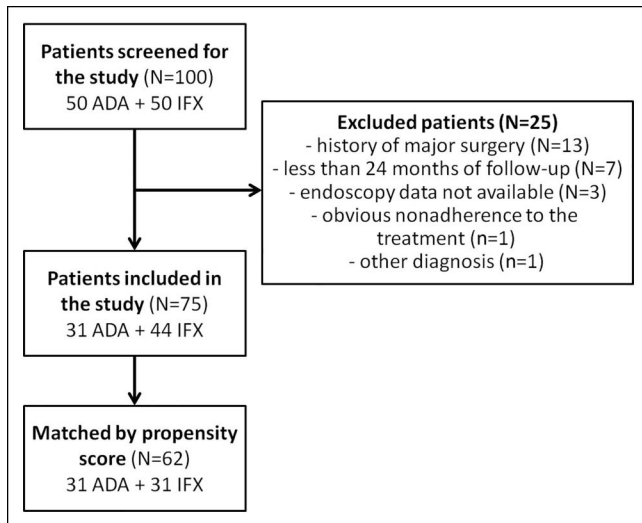
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Figure 1. Flowchart of patient recruitment into the study and propensity score matching.

to factors that could influence the outcome or choice of therapy. Matching was performed using nearest neighbor matching with a ratio of 1:1. The covariate balance in the matched sample was checked by visual inspection of plots showing the mean of each covariate against the estimated propensity score, separately by treatment status. The effect of concomitant IMM therapy was evaluated as the percentage of time on concomitant IMM out of the complete follow-up time, as a continuous variable, and as a categorical variable if the patient received IMM for at least 6 months.

The primary outcome of the study was evaluated using a Cox proportional hazards model, subsequently adjusted for the proportion of time on IMM therapy. The preselected predictors were tested using unadjusted Cox regression. To assess the importance of particular variables, we further tested the association of time to relapse with the variables using multivariable Cox proportional hazards models.

We used a generalized linear mixed model to assess the association between SAE and the type of anti-TNF therapy. All mixed models were adjusted for follow-up time and IMM use. When values were missing, the time point was omitted from the current analysis.

$P < 0.05$ was considered significant. A 95% confidence interval (CI) was used. Figures were constructed using R package ggplot2. According to powerSurfEpi R-package, our study with 31 experimental subjects and 31 control subjects was able to detect hazard ratio (HR) of < 0.34 or > 2.90 with probability (power) 0.80.

RESULTS

Of 100 patients screened for inclusion in the study (50 ADA and 50 IFX), 25 met the exclusion criteria. The basic characteristics of patients in each study group before propensity score matching (31 patients in the ADA group and 44 patients in the IFX group) are presented in Table 1. No significant differences were found, except for family history of inflammatory bowel disease (IBD), which was more frequent in the IFX group ($P = 0.03$). Finally, propensity score matching allowed us to directly compare 31 pairs of patients (Figure 1).

Primary outcome—time to treatment escalation

The overall time to treatment escalation in the whole study group (N = 75) is presented in Figure 2a, showing an approximate rate of 50% during the 3-year follow-up. Neither subanalysis of the whole study group (N = 75, HR = 0.68 [95% CI 0.35.1.33], $P = 0.26$, Figure 2b) nor of patients matched by propensity score (N = 62, HR = 0.63 [95% CI 0.31–1.28], $P = 0.20$, Figure 2c) revealed any significant difference in time to treatment escalation between ADA and IFX. The results were not affected by adjusting this model to concomitant IMM (HR = 0.63 [95% CI 0.31–1.28], $P = 0.20$).

When the need for treatment intensification was omitted (situation classified as relapse) (see Figure 3a for pooled data on ADA + IFX), there was no significant difference in relapse rate between the ADA and IFX groups, in the whole study group (N = 75, HR = 0.83 [95% CI 0.40–1.76], $P = 0.64$, Figure 3b), or
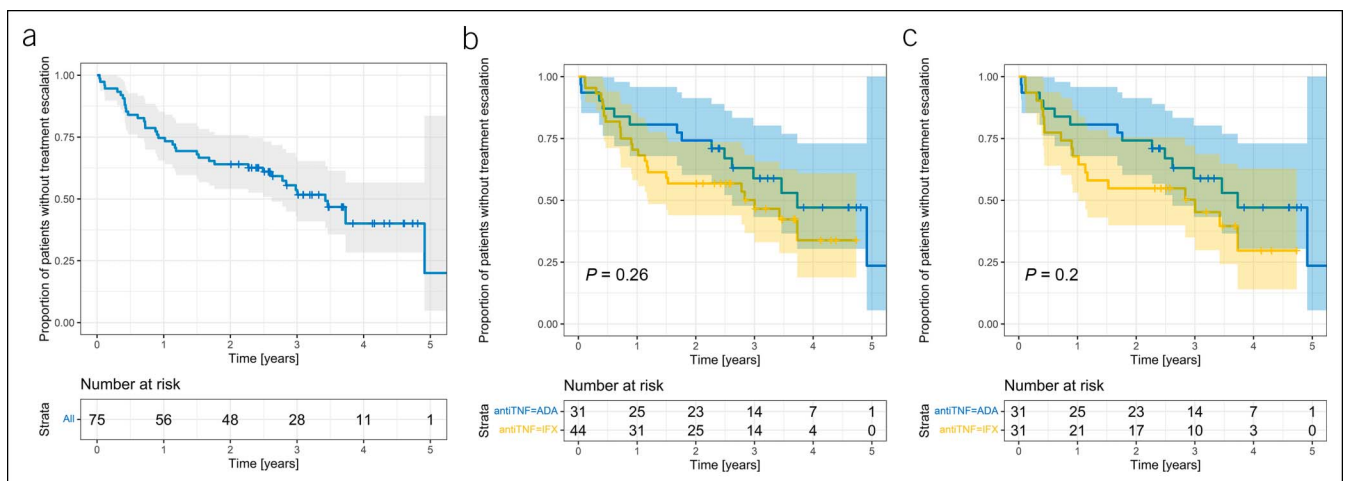

Figure 2. (**a**) Survival curve of time to treatment escalation in the whole study group (pooled data, N = 75). (**b**) Time to treatment escalation according to the type of anti-TNF therapy in the whole study group (N = 75). (**c**) Time to treatment escalation according to the type of anti-TNF therapy after propensity score matching (N = 62). ADA, adalimumab; IFX, infliximab; TNF, tumor necrosis factor.
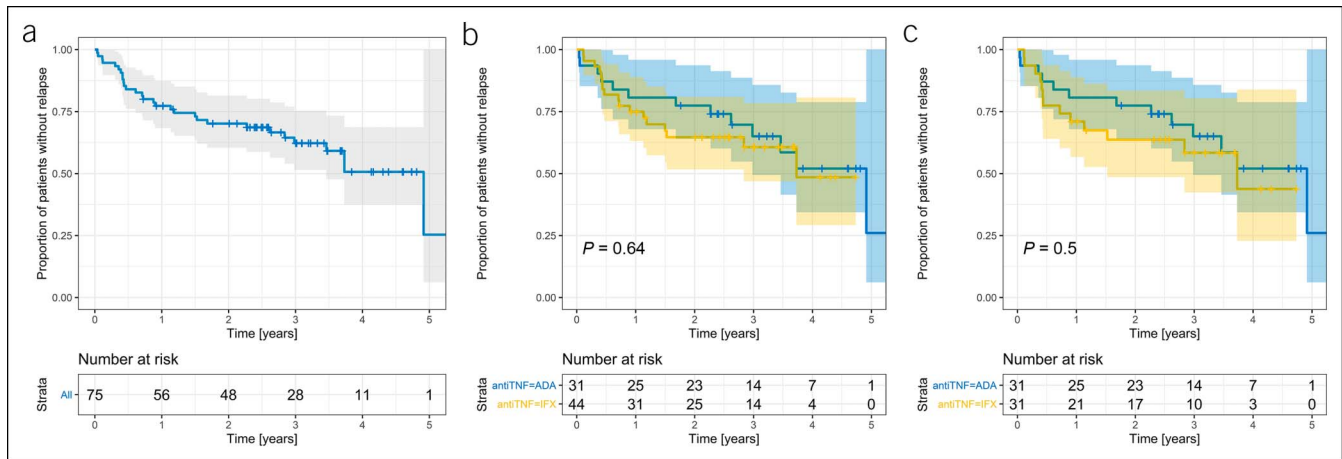
Figure 3. (**a**) Survival curve of time to relapse (when dose and interval adjustment were omitted as a reason) in the whole study group (pooled data, N = 75). (**b**) Time to relapse (when dose and interval adjustment were omitted as a reason) according to the type of anti-TNF therapy in the whole study group (N = 75). (**c**) Time to relapse (when dose and interval adjustment were omitted as a reason) according to the type of anti-TNF therapy after propensity score matching (N = 62). ADA, adalimumab; IFX, infliximab; TNF, tumor necrosis factor.

after propensity score matching (N = 62, HR = 0.76 [95% CI 0.35–1.68], P = 0.50, Figure 3c). Adjusting this model to concomitant IMM did not affect the results (HR = 0.76 [95% CI 0.34–1.67], P = 0.49).

Supplementary Digital Content (see Supplementary Table 2, http://links.lww.com/CTG/A800) presents various reasons for treatment escalation during the follow-up period in both groups after propensity score matching (N = 62). There was no significant difference between the 2 groups in any of the reasons listed.

Secondary outcomes

Primary nonresponse. There was no statistically significant difference in the primary nonresponse rate before propensity score matching (2/31 [6%] in the ADA group and 3/44 [7%] in the IFX group; P = 0.95) nor after matching (2/31 [6%] in the ADA group and 3/31 [10%] in the IFX group; P = 0.64). There was no significant difference in inflammatory markers (CRP, erythrocyte sedimentation rate, and F-CPT) or wPCDAI between ADA and IFX at the end of the induction period (week 12–16).

Predictors of treatment escalation and relapse. On a univariate analysis of the whole study group (N = 75, pooled data), anti-neutrophilic antibody (pANCA) positivity and anti-*Saccharomyces cerevisiae* antibody (ASCA) negativity were identified as potentially strong predictors of treatment escalation. The SES-CD, L3 disease phenotype, and use of concomitant IMM for at least the first 6 months demonstrated a trend toward significance (Table 2). In a subsequent multivariate analysis, the combination of ASCA negativity and pANCA positivity was identified as the only and very strong independent predictor of treatment escalation (HR 5.19, 95% CI 2.41.11.18, P < 0.0001, Figure 4). There was no effect of disease phenotype, concomitant IMM, or type of anti-TNF when added to the model (Table 3).

Predictors of relapse (as defined earlier) were similar to those of treatment escalation (L3, SES-CD, pANCA positivity, and B2 being statistically significant (P < 0.05) and L1, family history of IBD, and ASCA negativity being of borderline significance). A combination of pANCA and ASCA remained a strong predictor

(P = 0.0091). There was no effect of concomitant IMM or type of anti-TNF when added to the model.

SAEs. A comparison of SAE occurrence in the treatment groups before and after propensity score matching is summarized in Tables 4 and 5. No significant difference was identified between the ADA and IFX groups, except for pneumonia after propensity score matching (3 cases in the IFX group and no cases in the ADA group; P = 0.04). A subsequently performed mixed model reflecting the occurrence of SAEs during each patient visit and adjusted to concomitant IMM treatment and length of follow-up did not reveal any differences between the study groups (Table 6). In 1 patient receiving ADA, serious dermatological side effects led to cessation of ADA. In 1 patient receiving IFX, infusion allergic reaction led to the cessation of IFX.

PK. Regarding reactive TDM performed during the study period, TDM data were only available from selected visits (12% of all anti-TNF visits; 4% in the ADA group, and 21% in the IFX group). The median (IQR) trough levels at the time of the primary outcome were 14.05 (10.88–15.40) μg/mL in the ADA group and 6.15 (2.08–6.58) μg/mL in the IFX group (1 patient in the IFX group had undetectable trough levels). Positive ATI were only detected in the IFX group (5 observations in 3 patients during the follow-up period).

Because we did not intend to compare the PK of both anti-TNF agents, the PK subanalysis on propensity score–matched subgroups was not performed.

Concomitant IMM. After the onset of anti-TNF for at least 6 months, 29/31 (94%) patients in the ADA group and 38/44 (86%) in the IFX group received concomitant IMM therapy (97% AZA and 3% MTX). Adjusting the Cox model of time to treatment escalation (primary outcome) to concomitant IMM treatment did not affect the results (see the section on primary outcome). In the pooled data (N = 75), concomitant IMM (as a continuous or categorical variable) was not identified as a strong independent predictor of treatment escalation on either univariate or multivariate analysis (Table 2). Because only a minority of patients

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Table 2. Risk factors of treatment escalation identified by univariate analysis in the whole study group (N = 75)

	HR (95% CI)	*P* value
pANCA positivity	**3.221 (1.521–6.820)**	**0.002**
ASCA negativity	**3.093 (1.469–6.514)**	**0.003**
SES-CD	**0.960 (0.923–0.999)**	**0.045**
L3 phenotype	**0.571 (0.300–1.087)**	**0.088**
Concomitant IMM (at least 6 mo)	**0.472 (0.196–1.134)**	**0.093**
Concomitant immunopathology	0.197 (0.027–1.469)	0.113
B2 disease phenotype	2.011 (0.837–4.833)	0.118
Family history of IBD	1.892 (0.827–4.327)	0.131
L1 disease phenotype	1.580 (0.807–3.094)	0.182
Time to anti-TNF onset	1.213 (0.876–1.680)	0.244
F-CPT	1.000 (1.000–1.001)	0.249
Perianal disease	1.489 (0.749–2.962)	0.257
L2 disease phenotype	1.808 (0.553–5.907)	0.327
B1 disease phenotype	0.704 (0.331–1.497)	0.363
B3 disease phenotype	0.526 (0.122–2.260)	0.388
BMI *z* score	1.047 (0.901–1.218)	0.547
CRP	0.996 (0.982–1.010)	0.559
ESR	0.996 (0.982–1.010)	0.560
Growth impairment	1.213 (0.610–2.410)	0.582
Concomitant IMM (as continuous)	0.774 (0.286–2.092)	0.614
wPCDAI	0.995 (0.976–1.015)	0.616
Age	0.979 (0.875–1.096)	0.716
Sex (male)	0.907 (0.476–1.727)	0.766
Height *z* score	0.989 (0.919–1.065)	0.775
Albumin	1.005 (0.959–1.054)	0.826
Year of anti-TNF administration (era)	1.024 (0.721–1.453)	0.896
Smoking	0.945 (0.214–4.178)	0.941

Predictive factors were evaluated during anti-TNF onset. Values are listed as hazard ratio (HR) with 95% confidence interval (CI) and sorted by the raising *P*-value. In the multivariate model, factors in bold were tested, and composite predictive factor (pANCA+ and ASCA-) was used (Table 3).
ASCA, anti-*Saccharomyces cerevisiae* antibodies; BMI, body mass index; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; F-CPT, fecal calprotectin; IBD, inflammatory bowel disease; IMM, immunomodulators; pANCA, antineutrophilic antibodies; SES-CD, simple endoscopic score for Crohn's disease; TNF, tumor necrosis factor; wPCDAI, weighted pediatric Crohn's disease activity index.

received anti-TNF monotherapy, and limited PK data were available, a subanalysis investigating the effects of IMM on drug PK was not performed.

DISCUSSION

In accordance with guidelines on the management of pediatric CD, the selection of anti-TNF therapy (ADA vs IFX) in anti-TNF naive patients is based on patient and family preference, drug availability, administration route, and cost (10,11). This approach is based on early adult (mainly retrospective) studies that did not demonstrate any difference in efficacy between ADA and IFX (12–22), and subsequent large adult prospective studies (23,24) and retrospective studies with the longest follow-up to date (up to 5 years) (25,26). Beyond clinical efficacy, no difference was found in mucosal and histological healing (27). Two recent large propensity score–matched comparison studies in adult patients revealed no significant difference in clinical benefit between the 2 therapies. In addition, large nationwide population-based studies revealed no differences in real-world settings (28,29). Even studies showing some differences do not consistently demonstrate an effect in one direction (30–34). Thus, to date, there is no firm evidence that initiating either ADA or IFX in anti-TNF naive adult patients would make a difference, even for long-term prognosis (a median follow-up of 64 months) after switching to second-line anti-TNF (35). Neither a Markov model (3-month cycle) developed to simulate the therapeutic sequences of initiating biological treatment with ADA or IFX revealed any significant differences in persistence after 3 years in patients with active luminal CD (36).

Along with anti-TNF agents, anti-integrins and anti-IL 12/23 biologics have been proven by RCTs to be effective in adults with active CD (37). Because head-to-head trials would require a high number of patients for a noninferiority design and are unlikely to be performed unless funded by academic (nonindustry) institutes, indirect comparisons based on systematic reviews and network meta-analyses may help clinicians to guide first-line biological treatment. In the study by Singh et al. (7), both ADA and IFX were ranked highest among all biologicals as first-line therapy for the induction of remission in adult patients with moderate to severe CD confirming the results of a previous network meta-analysis evaluating various biologics in both the induction and maintenance phases and including IMM as a comparator (3). By contrast, in an older network meta-analysis, despite both ADA and IFX being effective, IFX was found to have the highest probability of being ranked as the most efficacious agent for induction (86%) and ADA for the maintenance of remission (48%) (8).

In pediatric clinical practice, adult data are relied upon because evidence in children is very scarce. In previous RCTs, both ADA and IFX were shown to be effective and safe in pediatric populations (1,2). Early retrospective observational studies revealed no difference between both therapies for up to 3 years of follow-up after the induction phase (6). A recent systematic review and meta-analysis identified 4 prospective cohort studies comparing ADA and IFX in pediatric populations (4). Three of these were abstracts; the only study that was published as a full text evaluated mucosal healing with anti-TNF therapy in 37 patients (12 ADA and 25 IFX) with biologically naive CD (5). No significant difference was found between the 2 therapies in achieving complete mucosal healing over 1 year of follow-up (*P* = 0.74). High rates of clinical benefit (remission + response 65%–93%) within 2 years of follow-up with no significant difference between ADA and IFX were recently reported among 87 children with CD from a prospective cohort of the Sicilian IBD Network (9).

Thus, to date, there is no evidence that ADA is superior to IFX or vice versa in adult or pediatric patients with CD (38). This is also supported by our data based on propensity score matching. However, our power calculations showed that using 31 experimental and 31 control subjects, we were not able to detect HR of approximately 0.34–2.90. Thus, we can only conclude that there
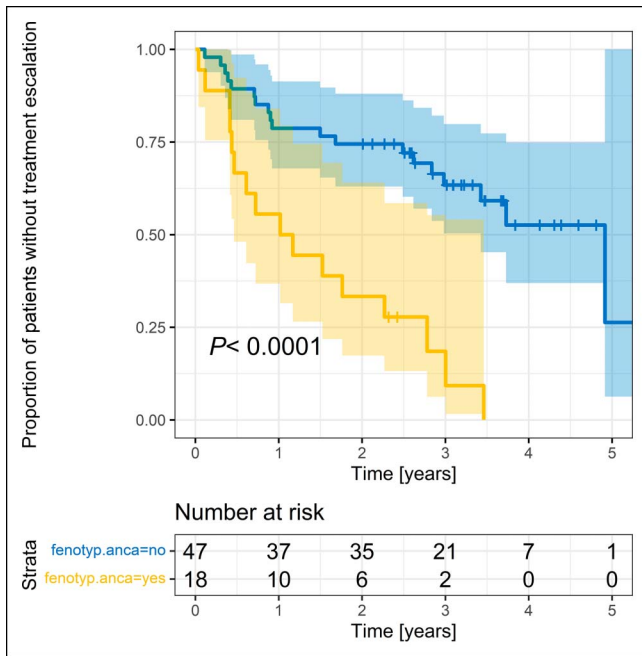
Figure 4. Time to dose and interval adjustment in the whole study group (pooled data, N = 75) stratified by composite predictor (combination of ASCA negativity and pANCA positivity [fenotyp ANCA = yes] vs combination of ASCA positivity and pANCA negativity [fenotyp ANCA = no]). ASCA, anti-*Saccharomyces cerevisiae* antibodies; pANCA, antineutrophilic antibodies.

does not seem to be a substantial difference in the efficacy of both drugs.

Nevertheless, in real-life clinical practice, ADA is often considered as a second-line anti-TNF therapy in pediatric patients (39,40). This may be based on historically stronger experience with IFX, which, for many years, has been the only anti-TNF therapy approved for pediatric patients with CD. IFX may also be perceived as being more potent and adjustable than ADA by some clinicians due to the intravenous route of administration and weight-based dosing schedule, which allows a more precise dosage, especially in smaller children (41). In perianal disease, IFX may be preferred in clinical practice; however, available data probably do not allow first-line anti-TNF therapy to be determined based on disease phenotype (24,38,42,43).

The overall time to treatment escalation in our study was approximately 50% within 3 years of follow-up. However, our definition of treatment escalation also included the need for dose and interval adjustment, which increases the rates compared with a recently published systematic review of pediatric cohort studies reporting the probability of continuing IFX therapy 83%–97% after 1 year and 67%–91% and 61%–85% after 2 and 3 years, respectively. No conclusions can be made for ADA in this review due to the limited number of time-to-event studies (44). When we omitted the need for dose and interval adjustment from the definition, our relapse rate was similar (40% during 3 years) to those published. In the study focused on loss of response in primary responders, the reported random effects pooled incidence of dose intensification was 38% (95% CI 28–50) for IFX and 36% (95% CI 30–43) for ADA, with substantial heterogeneity in both cases. In pediatric patients, the mean percentage loss of response was 25.5%, with no possibility to compare anti-TNFs because of the lack of data (45).

Primary nonresponse to anti-TNF therapy is a substantial obstacle in IBD treatment, especially in adults, and is associated with an inferior response to second-line biologics (7). Primary nonresponse rates in our study (6% with the ADA group and 7% with the IFX group) were lower than those reported for both adults and children (1,2,37). However, these rates do not seem to be underestimated because the inflammatory markers and wPCDAI significantly decreased in both groups up to week 12–16. It is unlikely that patients would continue anti-TNF therapy due to the physicians' decision despite any signs of improvement. Moreover, nonresponse rates may be higher in RCTs, which follow a strict protocol, and different definitions of nonresponse are used in various studies, preventing direct comparison of results. Furthermore, a recently proposed tight TDM strategy during the induction phase (11), which could identify early nonresponders by PK, was not performed in our Center during the study. Several predictors of primary nonresponse are described in the literature (38,46); however, we did not perform these analyses because the rates of primary nonresponse were very low in our patient population.

Concerning predictors of long-term anti-TNF response, traditional factors that appear in the literature, and are derived mainly from adult data are younger age (younger than 40 years), being naive to anti-TNF, and concomitant use of IMM (38). In our study, only the latter was considered relevant and is discussed further. In pediatric patients, these data are generally very scarce.

Table 3. Risk factors of treatment escalation tested by multivariate analysis in the whole study group (N = 75)

	HR (95% CI)	*P* value	Significance
pANCA+ and ASCA−	5.19 (2.41–11.18)	0.00003	***
L3 phenotype	0.49 (0.23–1.07)	0.073	NS
SES-CD	0.98 (0.94–1.03)	0.523	NS
Concomitant IMM (at least 6 mo)	0.78 (0.27–2.28)	0.650	NS
Type of anti-TNF	0.95 (0.45–2.03)	0.901	NS

Predictive factors were evaluated during anti-TNF onset (Table 2). Values are listed as hazard ratio (HR) with 95% confidence interval (CI) and sorted by the raising *P*-value. In the multivariate model, factors in bold were tested, and composite predictive factor (pANCA+ and ASCA−) was used (Table 3).
ASCA, anti-*Saccharomyces cerevisiae* antibodies; CI, confidence interval; HR, hazard ratio; IMM, immunomodulators; pANCA, antineutrophilic antibodies; SES-CD, simple endoscopic score for Crohn's disease; TNF, tumor necrosis factor.
***p<0.001; NS = not significant.

Table 4. SAE according to the treatment group before propensity score matching (N = 75)

	ADA (N = 31)	IFX (N = 44)	*P* value
Pneumonia	0 (0), NA = 0	3 (0.07), NA = 0	0.07
Meningitis	0 (0), NA = 0	2 (0.05), NA = 0	0.14
Pancreatitis	0 (0), NA = 0	2 (0.05), NA = 0	0.14
Leukopenia	1 (0.03), NA = 0	2 (0.05), NA = 0	0.77
Anemia	2 (0.06), NA = 0	4 (0.09), NA = 0	0.67
HSV	3 (0.1), NA = 0	6 (0.14), NA = 0	0.6
VZV	2 (0.06), NA = 0	1 (0.02), NA = 0	0.37
Other	12 (0.39), NA = 0	15 (0.34), NA = 0	0.68
Hospitalization	14 (0.45), NA = 0	15 (0.34), NA = 0	0.33
Any SAE	20 (0.65), NA = 0	29 (0.66), NA = 0	0.9

ADA, adalimumab; HSV, herpes simplex virus; IFX, infliximab; SAE, serious adverse event; VZV, varicella zoster virus.

A recently published study within the pediatric inflammatory bowel disease (PIBD) Ahead project identified several risk factors (especially phenotypic, serological, and genetic) for unfavorable disease course; however, predictors of anti-TNF response/relapse were not specifically addressed (47). In the largest pediatric prospective inception cohort study (RISK study) in 913 CD patients, several risk factors of B2 and B3 disease behavior were identified but with no specific conclusions regarding the prediction of anti-TNF efficacy (48). Recent studies identified various serological or genetic predictors of anti-TNF response (49–54); however, these factors were not measured in our patients and thus cannot be discussed. We identified a combination of ASCA negativity and pANCA positivity as the strongest independent predictors of treatment escalation in the multivariate model. To the best of our knowledge, this serological combination has not previously been described in the literature and should be prospectively validated in an independent cohort. Because pANCA positivity is typical for the ulcerative colitis (UC)-like phenotype, and anti-TNF effectivity is generally lower in UC than in CD (9,12), it remains unclear whether the abovementioned serological combination could be a potential proxy marker of distinct disease phenotype of CD with lower sensitivity to anti-TNF treatment.

Based on the results of a network meta-analysis focused on the side effects of anti-TNF, the relative safety profiles of ADA and IFX seem to be comparable (55). In our study, SAE rates were low, did not differ between both groups in the mixed model, and led only occasionally to treatment cessation (only 1 patient in each group), supporting the current opinion that anti-TNF treatment is safe in pediatric CD. Neither a recently published nationwide cohort study among 2018 pediatric IBD patients revealed any association between anti-TNF use and the risk of serious infections (56,57).

Proactive TDM was not performed in our study; thus, limited data did not allow us to fully evaluate the predictive value of PK regarding anti-TNF response. However, data available from selected visits have revealed median levels of both ADA and IFX in the range of recent recommendations in pediatric patients (11). Thus, it is unlikely that our patients were underdosed and that the physicians' approach was affected by this phenomenon. ATI formation was very rare but the transient presence of ATI could have been overlooked due to the reactive TDM approach. Recent studies identified various predictors of IFX levels, such as the presence of ATI, serum albumin concentration, concomitant IMM therapy, body weight, and sex (58). Owing to the scarcity of

Table 5. SAE according to the treatment group after propensity score matching (N = 62)

	ADA (N = 31)	IFX (N = 31)	*P* value
Pneumonia	0 (0), NA = 0	3 (0.1), NA = 0	0.04
Meningitis	0 (0), NA = 0	1 (0.03), NA = 0	0.24
Pancreatitis	0 (0), NA = 0	2 (0.06), NA = 0	0.09
Leukopenia	1 (0.03), NA = 0	0 (0), NA = 0	0.24
Anemia	2 (0.06), NA = 0	4 (0.13), NA = 0	0.39
HSV	3 (0.1), NA = 0	4 (0.13), NA = 0	0.69
VZV	2 (0.06), NA = 0	1 (0.03), NA = 0	0.55
Other	12 (0.39), NA = 0	11 (0.35), NA = 0	0.79
Hospitalization	14 (0.45), NA = 0	10 (0.32), NA = 0	0.3
Any SAE	20 (0.65), NA = 0	22 (0.71), NA = 0	0.59

ADA, adalimumab; HSV, herpes simplex virus; IFX, infliximab; SAE, serious adverse event; VZV, varicella zoster virus.

Table 6. Mix model presenting occurrence of any SAE—adjusted to type of anti-TNF, concomitant IMM, and length of follow-up

	OR (95% CI)	*P* value
Type of anti-TNF	1.072 (0.566–2.031)	0.831
Concomitant IMM	1.613 (0.627–4.148)	0.322
Length of follow-up	1.167 (0.934–1.459)	0.175

Numbers in Tables 4 and 5 are listed as No. (and fraction, %) of cases that presented with respective SAE at least once during the follow-up. There were no cases of hepatopathy, thrombosis, malignancies, or deaths identified in any of the groups. The subsequently performed mix model (Table 6) did not find any difference in the occurrence of SAE between both groups.
CI, confidence interval; IMM, immunomodulator; SAE, serious adverse event; TNF, tumor necrosis factor.

PK data in our study, we did not intend to identify any predictors of PK in our patients.

The approach to concomitant IMM therapy differs among pediatric IBD centers. In the European Union, AZA is used in most patients; by contrast, in the United States, use of MTX or anti-TNF monotherapy is more popular (39,59). Despite conflicting data, combination therapy is still considered useful (13,60–63), and most pediatric centers use it for at least 6 months from the onset of anti-TNF treatment. In accordance with recent data and current guidelines, IMM has been used less frequently in patients treated with ADA compared with patients treated with IFX (11,64). In our study, IMM treatment was not identified as a strong predictor of relapse on both univariate and multivariate analyses. These results could be affected by the high rate of concomitant IMM treatment in both groups. Owing to limited data, we could not analyze the possible effect of IMM on anti-TNF PK.

In addition to efficacy and safety, cost may be an important factor when selecting an appropriate first-line anti-TNF therapy. In some studies, ADA seems to be less costly than IFX; in others, the opposite seems to be true (65–68). Moreover, biosimilars coming to the market have changed the scenario significantly (69,70). Financial issues may be strongly dependent on the local situation, and other aspects such as quality of life should be considered when selecting an appropriate biological treatment.

Our data show that both ADA and IFX seem to demonstrate comparable efficacy and safety in pediatric CD patients naive to biologics. This study included a relatively small sample size compared with adult trials, preventing us from drawing strong conclusions. Despite its prospective design, some data were missing, and PK data were not available at all time points because TDM was not applied proactively during the study. Results in ADA-treated patients may have been influenced by a lack of adherence to therapy, which we were unable to evaluate. Conversely, this is the first pediatric study using propensity score matching with effective pairing (no dropouts), a prospective design, and a long duration of follow-up. Data comparing both anti-TNFs should be considered with caution in the future because these are derived from the traditional step-up approach. Because the top-down strategy (at least for IFX) may become preferable in children based on recent data (11,71), further research on the efficacy of various biologics as first-line treatment immediately after diagnosis must be performed.

CONFLICTS OF INTEREST

ACKNOWLEDGEMENT

Study Highlights

WHAT IS KNOWN

✓ Both adalimumab (ADA) and infliximab (IFX) are effective and safe in the treatment of pediatric Crohn's disease.

WHAT IS NEW HERE

✓ This is the first prospective observational study comparing ADA and IFX in pediatric Crohn's disease.

✓ Propensity score matching did not reveal substantial differences in efficacy or safety between ADA and IFX.

✓ The ASCA−/pANCA+ combination is a strong predictor of treatment escalation.

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