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Efficacy of Infliximab Biosimilar for Maintenance Therapy in Pediatric Inflammatory Bowel Disease Following Infliximab Originator

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Objectives: The safety, efficacy, and cost-effectiveness of Infliximab biosimilar agents in the management of inflammatory bowel disease in adults have been shown. These agents have been recommended for pediatric inflammatory bowel disease, and although institutions are initiating therapy with the biosimilar agents (IFX-B), few are switching maintenance therapy from the originator (IFX-O). The aim was to compare biochemical markers of disease activity of children with inflammatory bowel disease on maintenance therapy with IFX-B to their previous markers on IFX-O.

Methods: Single-center, retrospective chart review of 25 children with inflammatory bowel disease who transitioned from Remicade (IFX-O) to the biosimilar agent Inflectra (IFX-B) for maintenance therapy. Analysis included demographics and various biochemical markers of disease control. The nonparametric-related samples Wilcoxon signed-rank test was used to compare mean ranks of these markers (C-reactive protein, erythrocyte sedimentation rate, hemoglobin, platelet count, albumin, body mass index *z* score) between the last 12 months on IFX-O and the first 12 months on IFX-B.

Results: Between March 2018 and June 2018, the majority of patients with pediatric inflammatory bowel disease on maintenance therapy with IFX-O at our institution were transitioned to maintenance therapy with IFX-B. Of the 25 children included, 17 were diagnosed with Crohn disease and 8 with ulcerative colitis. The results of all, except albumin value, supported retention of the null hypothesis that there would not be a statistically significant difference in the biochemical markers of disease activity between the 2 medications.

Conclusions: IFX-B is as effective as IFX-O for maintenance therapy in pediatric inflammatory bowel disease when comparing biochemical markers of disease activity.

Key Words: Remicade, Inflectra, Crohn disease, ulcerative colitis

What Is Known?

- Biologic therapy with anti-tumor necrosis factor monoclonal antibodies is effective and safe for the treatment of pediatric inflammatory bowel disease.
- Transitioning from the Infliximab originator to biosimilar agents in adults has resulted in adequate disease control.

What Is New?

- Transitioning children on maintenance therapy with Remicade to a biosimilar agent results in similar values of biochemical markers of disease activity.
- Children can continue to have optimal growth when Infliximab biosimilar agents are used instead of the originator.

INTRODUCTION

Pediatric inflammatory bowel disease (IBD) includes Crohn disease (CD), ulcerative colitis (UC), and indeterminate IBD. Treatment is aimed at decreasing inflammation, achieving mucosal healing, maintaining disease control, reducing symptoms, and achieving ideal growth (19). Biologic therapy with anti-tumor necrosis factor (anti-TNF) monoclonal antibodies has been used to treat IBD in adults since the approval of Remicade (IFX-O) for the treatment of CD in 1998 (19). Since then, approval has been added for the use of anti-TNF agents for UC in adults, and CD and UC in pediatric patients.

Although the anti-TNF agents are highly effective in the treatment of IBD (19), these medications are expensive, and longer duration of use is expected when therapy is initiated during childhood. In 2012, with the loss of patent protection, the first Infliximab biosimilar agent (CT-P13) was developed and approved for use in the United States in 2016 (7). It is estimated that the cost of anti-TNF therapy in IBD can be reduced by 30%–70% with the use of the less expensive, biosimilar agents (6). Although the safety, efficacy and cost-effectiveness of Infliximab biosimilar agents (IFX-B) has been shown in adults, and the Food and Drug Administration has approved IFX-B for pediatric CD since 2016, data in the pediatric population continue to be limited, especially in the United States (2). Pediatric studies have looked at achieving disease remission using IFX-B, but no study has been completed in the United States looking at a study group that was switched from IFX-O to IFX-B while receiving maintenance infusions.

METHODS

Patient Selection

Following approval from the Wayne State University institutional review board, a retrospective chart review was performed at the Children's Hospital of Michigan, a member of the Detroit Medical Center. The review encompassed pediatric patients (<21 years of age) with IBD who received biological therapy with both IFX-O, the Infliximab originator, and Inflectra (IFX-B), the Infliximab biosimilar agent. To be included, duration of therapy on both medications

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had to be at least 12 months to allow for comparison. Patients who were not transitioned to IFX-B, those on IFX-O for <12 months prior to the medication change, and those on IFX-B for <12 months at the time of analysis were excluded from the study (Fig. 1).

Study Design

Data were collected by a single reviewer using a standardized form, including the patient's age at diagnosis, sex, diagnosis, age at initiation of biologic therapy with IFX-O, duration of time on IFX-O prior to transition, duration of time on IFX-B, laboratory values (C-reactive protein, erythrocyte sedimentation rate, hemoglobin, platelet count, albumin) and body mass index *z* scores, and additional medications administered over the 24 month period.

Statistical Analyses

Demographic and disease activity variables were compared between the 12 months receiving IFX-B as maintenance therapy and the previous 12 months receiving IFX-O. Age and durations were expressed in terms of years and months (days ≥15 were rounded up to 1 month). The mean ranks of the various disease markers for the time on IFX-O and the time on IFX-B were compared using the nonparametric-related samples Wilcoxon signed-rank test (Table 1). A $P < 0.05$ was deemed statistically significant.

RESULTS

Patient Characteristics

Seventy-eight potential subjects were receiving IFX-O at the time of data collection, and 25 were included in the final analysis. Twenty-seven had not transitioned to IFX-B, 4 were transitioned from IFX-O to vedolizumab, 9 received IFX-O for <12 months prior to the medication change, 11 received IFX-B for <12 months at the time of data collection, and 2 patients were 21 years of age or older before completing 12 months on IFX-B. Demographic details of the 25 patients that met inclusion criteria were summarized (Table 2).

Clinical Outcomes

No clinically significant differences in the majority of biochemical markers of disease activity (C-reactive protein, erythrocyte sedimentation rate, hemoglobin, platelet count) or in body mass index *z* score were found when comparing the last 12 months the patients received IFX-O to the first 12 months they received IFX-B (Table 1). Albumin values did differ ($P = 0.000$). The majority of the laboratory tests were obtained at the time the patients received their infusions and not at the time of their visits to clinic. Thus, symptoms were not assessed at the time the labs were drawn, and therefore the Pediatric Ulcerative Colitis Activity Index and Pediatric Crohn's Disease Activity Index scores could not accurately be used in this study.

In addition to the analyzed disease markers, hospital admissions, treatment for *Clostridium difficile* infection, need for adjunct corticosteroid therapy, and requirement for higher doses of biologic medications are also important considerations. The number of patients requiring these various interventions was compiled for the last 12 months the patients received IFX-O and for the first 12 months, they received IFX-B (Table 3), and the results are nearly identical.

DISCUSSION

This retrospective study provides an analysis of various biochemical markers of disease activity in 25 pediatric patients with IBD who were receiving IFX-O for maintenance therapy and were transitioned to the biosimilar agent IFX-B over a 3-month period. Our results indicate that over a 12-month follow up period, transitioning therapy from IFX-O to IFX-B in pediatric patients with IBD

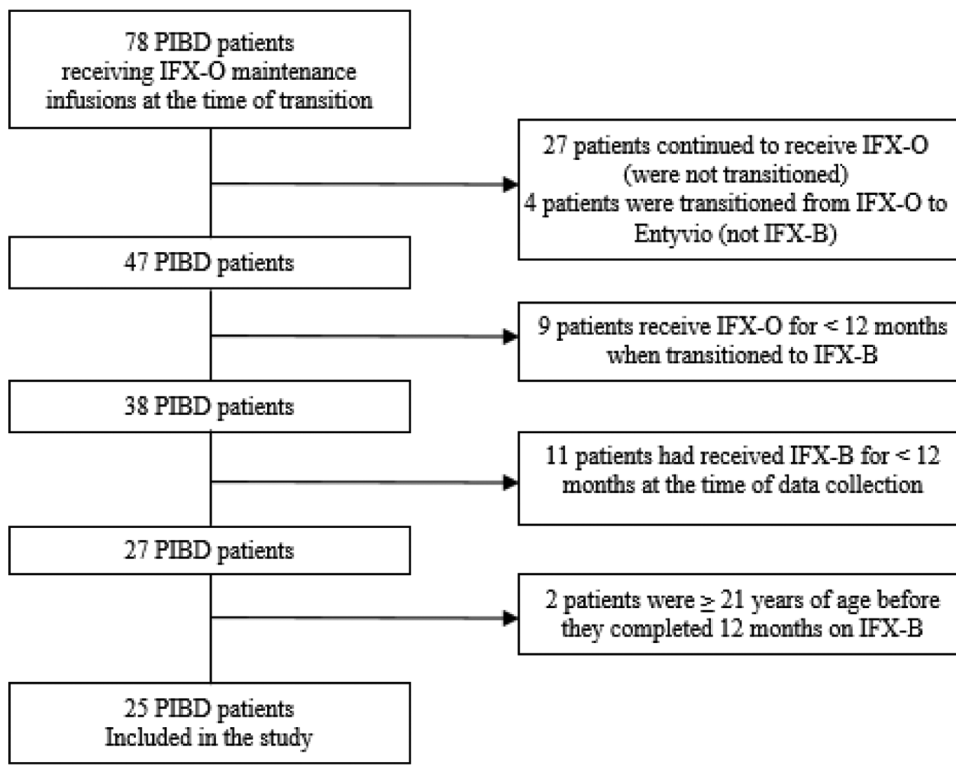

FIGURE 1. Flow diagram showing patient selection. IFX-B = Infliximab biosimilar; IFX-O = Infliximab originator; PIBD = pediatric inflammatory bowel disease.

TABLE 1. Comparison of disease markers between the last 12 months on IFX-O for maintenance therapy compared with the first 12 months on IFX-B

		Last 12 mo receiving IFX-O		First 12 mo receiving IFX-B		
Variable	**Reference range**	**Mean (n = 25)**	**SD**	**Mean (n = 25)**	**SD**	***P* (2-tailed)**
CRP (mg/L)	<5.0	9.712	14.8330	10.736	12.4386	0.353
ESR (mm/h)	0–13	16.744	12.8279	17.704	16.1983	0.607
Hemoglobin (g/dL)	11.7–15.9	13.008	1.6560	12.924	1.9541	0.989
Platelet count (K/CUMM)	130–450	329.956	87.9698	321.168	85.4854	0.137
Albumin (g/dL)	3.9–4.9	3.953	0.4334	4.409	0.6972	0.000
BMI (kg/m^2)		0.266	0.9953	0.265	1.1593	0.411

BMI = body mass index; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; IFX-B = Infliximab biosimilar; IFX-O = Infliximab originator.

TABLE 2. Patient characteristics

Variable		n (%)
Gender	Male	16/25 (64%)
	Female	9/25 (36%)
IBD classification	Crohn disease	17/25 (68%)
	Ulcerative colitis	8/25 (32%)
	Mean (y + mo)	Median (IQR) (y + mo)
Age at time of IBD diagnosis	10 + 11	11 + 8 (8 + 0, 13 + 10)
Age at time of IFX-O initiation	12 + 0	12 + 4 (9 + 4, 14 + 8)
Age at time of transition from IFX-O to IFX-B	15 + 8	16 + 9 (13 + 9, 17 + 11)
	Mean (mo)	Median (IQR) (mo)
Time from IBD diagnosis to IFX-O initiation	12	8 (1–20)
Time on IFX- prior to transition to IFX-B	46	37 (26–71)

IBD = inflammatory bowel disease; IFX-B = Infliximab biosimilar; IFX-O = Infliximab originator; IQR = interquartile range.

TABLE 3. Details of other variables for comparison between the last 12 months on IFX-O for maintenance therapy compared with the first 12 months on IFX-B

	Last 12 mo receiving IFX-O	**First 12 mo receiving IFX-B**
Variable	**No. of patients**	**No. of patients**
Received combination therapy	16	16
Received antibiotics	1	1
Received corticosteroids	2	2
Tested + for *Clostridium difficile* infection	6	5
Required hospital admission	5	4
Infliximab dose was increased	5 (IFX-O)	3 (IFX-B)
Infliximab dose was decreased	2 (IFX-O)	3 (IFX-B)
Late or missed infusion(s)	4	4

IFX-B = Infliximab biosimilar; IFX-O = Infliximab originator.

on maintenance infusions is efficacious. The only result that did not support the null hypothesis was the albumin value. The result may be due to the small numerical value of this laboratory test. When comparing the mean values between the time receiving IFX-O to the time receiving IFX-B, the value is actually higher for the biosimilar group. Therefore, if the significant *P* value is real and not due to the small numerical value, the result actually favors IFX-B over IFX-O.

Numerous studies have been published on the safety and efficacy of biosimilars in the management of adults with IBD (5–7). Studies have also been reported in pediatric patients comparing induction of remission with IFX-O versus IFX-B and switching patients from IFX-O to IFX-B once biological therapy has already been started (1–4), but the latter have been conducted outside the United States. This is one of the first reports of a group of pediatric IBD patients in the United States that examines the level of disease activity (determined by biochemical markers) when their medication is transitioned from IFX-O to IFX-B.

Our results are similar to those reported in various pediatric studies out of Scotland (2), Poland and South Korea (3). Although numerous adult studies and these pediatric studies from outside of the United States have demonstrated that biosimilars are safe and effective, most centers across the United States are not transitioning their pediatric patients from IFX-O to IFX-B. Not only does this transition maintain consistency in these biochemical markers, it is also more cost effective. Additional data collected in our study assessing the number of hospital admissions, need for adjunct corticosteroid or antibiotic use, number of *C. difficile* infections, and the need to change the dose of medication was largely identical for the time on IFX-O compared with IFX-B.

The results of this study are limited by sample size, the single-center data analyzed, and the retrospective nature of the study. Additionally, because the laboratory values were obtained at times that

did not coincide with clinic visits, the Pediatric Ulcerative Colitis Activity Index and Pediatric Crohn's Disease Activity Index scores could not be determined. Additionally, other biochemical markers, for example, fecal calprotectin, were not routinely measured during the time these data were collected. We also did not evaluate the immunogenicity between the 2 medications. Furthermore, we only evaluated those receiving maintenance infusions and did not compare the medications with respect to induction of disease remission.

In the future, we would like to analyze the frequency of reported infusion reactions between IFX-O and IFX-B. It is possible the use of biosimilar agents is not only efficacious and cost effective but also safer.

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