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ORIGINAL ARTICLE

Gastroenterology: Inflammatory Bowel Disease

Clinical impacts of immunomodulator withdrawal from anti-tumor necrosis factor combination therapy in pediatric inflammatory bowel disease

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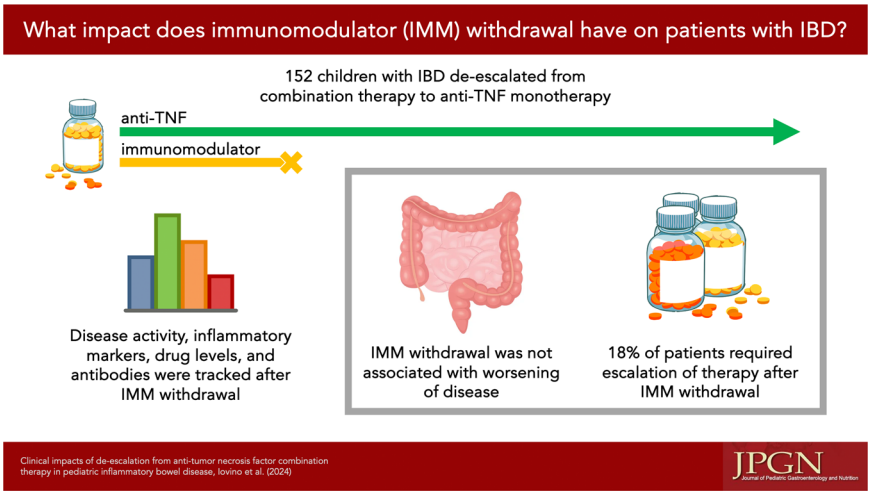
Abstract

Objectives: Combination therapy consists of both anti-tumor necrosis factor (anti-TNF) and an immunomodulator (IMM) and has been shown to improve outcomes in patients with inflammatory bowel disease (IBD). This study assesses the impacts of IMM withdrawal from combination therapy to anti-TNF monotherapy in children with IBD.

Methods: This single-center retrospective cohort study included children with IBD initiated on combination therapy between 2014 and 2019 who discontinued the IMM. We evaluated whether IMM withdrawal impacts laboratory values and disease activity. Linear mixed effects models with random intercepts were used to compare differences between groups. Chi-square and Kruskal–Wallis tests were used for comparisons between patients who did and did not require subsequent escalation of therapy.

Results: One hundred and fifty-two patients discontinued the IMM which did not significantly affect disease activity. However, 18% of patients escalated therapy after IMM withdrawal, primarily due to low anti-TNF levels. Lower anti-TNF and higher erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels before IMM withdrawal were associated with subsequent escalation of therapy. Overall, there was no statistically significant effect on anti-TNF drug levels. Patients with Crohn's disease (CD) on infliximab (IFX) and methotrexate (MTX) who discontinued the IMM had an increase in mean ESR and CRP ($p < 0.05$).

Conclusions: IMM withdrawal from anti-TNF combination therapy may be considered safe in the setting of higher anti-TNF levels and normal serum inflammatory markers. Clinicians should consider assessing anti-TNF levels and inflammatory markers after IMM withdrawal, especially in patients with CD receiving IFX who discontinued MTX.



KEYWORDS
biologic, de-escalation, monotherapy, therapeutics

1 | INTRODUCTION

There are over 3 million people in the United States diagnosed with inflammatory bowel disease (IBD), and upwards of 30% are diagnosed before the age of 20.[1,2] The incidence and prevalence of IBD continue to increase in pediatrics, and therefore safe and reliable treatments are needed.[3] Combination therapy refers to the use of a monoclonal antibody against tumor necrosis factor (anti-TNF), such as infliximab (IFX) or adalimumab, and an immunomodulator (IMM), such as methotrexate (MTX) or thiopurine (azathioprine [AZA] or 6-mercaptopurine [6MP]). Combination therapy has been shown to improve anti-TNF levels, decrease anti-TNF antibodies, decrease the risk of loss of response, and increase corticosteroid-free remission in children and adults with IBD.[4–12] Despite its benefits, exposure to combination therapy has been shown to increase the risk of IMM-related adverse events such as bone marrow suppression, opportunistic infection, and malignancy.[13–15] As a result, IMM withdrawal from anti-TNF combination therapy is often done to mitigate these risks. Several adult studies have found that IMM withdrawal had no significant effect on clinical outcomes,[16–18] but patients were more likely to develop anti-TNF antibodies and require anti-TNF dose escalation compared to patients continuing combination therapy.[16] There is limited research on the effects of IMM withdrawal in children with IBD.[19] Therefore, this study assesses the clinical impacts of IMM withdrawal and evaluates factors associated with subsequent escalation of therapy in children with IBD.

What is Known

- Combination therapy with an anti-tumor necrosis factor (anti-TNF) and immunomodulator (IMM) is an effective treatment for pediatric inflammatory bowel disease (IBD).
- IMMs are often discontinued to avoid adverse events.
- Limited data exist assessing the impacts of IMM withdrawal on children with IBD.

What is New

- IMM withdrawal was not associated with worsening clinical disease activity.
- Lower anti-TNF levels and higher sedimentation rate and C-reactive protein levels before IMM withdrawal may increase the risk for suboptimal response to subsequent anti-TNF monotherapy.
- Patients with Crohn's disease on infliximab who discontinued methotrexate had an increase in serum inflammatory markers.

2 | METHODS

2.1 | Population and study design

This was a single-center retrospective cohort study of pediatric patients with IBD, including Crohn's disease

(CD), ulcerative colitis (UC), and IBD-unclassified (IBD-U), whom were less than 18 years old when initiated on combination therapy (IFX/adalimumab + IMM) between January 1, 2014 and December 31, 2019. Patients with UC and IBD-U were grouped together for analysis. All patients were from Nationwide Children's Hospital (NCH), a tertiary center in Columbus, Ohio. Those meeting inclusion criteria were identified using historical data from the NCH Center for Pediatric and Adolescent IBD internal database. Included patients must have initiated the IMM no more than 60 days after beginning anti-TNF therapy. Patients must have also been on combination therapy for at least nine consecutive months before discontinuing the IMM and continuing anti-TNF monotherapy. Any patient not meeting these criteria was excluded. Institutional Review Board approval was obtained at NCH in Columbus, OH (STUDY0000341).

2.2 | Data collection and procedures

Data of patients meeting inclusion and exclusion criteria were reviewed. Patient demographics, disease phenotype, disease location and behavior (PARIS classification),[20] medication regimens, laboratory data (albumin [Alb], hemoglobin [Hgb], erythrocyte sedimentation rate [ESR], C-reactive protein [CRP], calprotectin, anti-TNF trough levels, and anti-drug antibodies against anti-TNF [ADA] (ARUP Laboratories, Salt Lake, UT)), short pediatric CD activity index (sPCDAI), and pediatric UC activity index (PUCAI) were collected at two time points: at or before IMM withdrawal (pre-stop) and 6–12 months after IMM withdrawal (post-stop).

Pre-stop data were collected at the closest available date to IMM withdrawal (within the 3 months leading up to or 14 days following IMM withdrawal). Thus, pre-stop data includes information gathered from patients no sooner than 6 months after initiating combination therapy. Post-stop data were collected 6–12 months after IMM withdrawal, with prioritization of data collection at 6 months. If there was an adjustment of therapy during the post-stop period, laboratory values and disease activity were recorded at the nearest available time point to the date of the change, even if sooner than 6 months after IMM withdrawal. Decisions to discontinue the IMM were not based on institutional guidelines but rather provider discretion. Decisions regarding post-stop adjustments to therapy, which included changes to anti-TNF dosage or frequency, restarting the IMM, switching from the anti-TNF to an alternative medication, or discontinuing the anti-TNF altogether, were also made at the discretion of the provider.

Reasons for adjustments to therapy were based on provider documentation and categorized as low anti-TNF levels, high anti-TNF levels, ADA, worsening of disease, adverse event, or patient preference. Any adjustment involving an increase in anti-TNF dosage or frequency, restarting the IMM, or switching from the anti-TNF to an alternative medication during the 12-month period following IMM withdrawal was recorded as a post-stop escalation of therapy. Consensus criteria for therapeutic anti-TNF levels at NCH included >5 μg/mL for IFX and >7.5 μg/mL for adalimumab. If more than one adjustment to therapy occurred within the 12-month post-stop period, the data was collected only from the time point nearest to the adjustment occurring first. Clinical remission was defined as <10 based on the sPCDAI for CD and PUCAI for UC/IBD-U.[21–23]

2.3 | Outcomes

The primary outcome was impact of IMM withdrawal from anti-TNF combination therapy on sPCDAI or PUCAI and laboratory markers 6 months after IMM withdrawal. Secondary outcomes included the effects of IMM withdrawal on anti-TNF trough levels, ADA development, and subsequent adjustments to therapy. An additional outcome of interest was comparison of factors among patients requiring post-stop escalation of therapy versus patients not requiring post-stop escalation of therapy.

2.4 | Statistical analysis

Linear mixed effects models with random intercepts accounting for correlated measures within a patient across time were used to compare pre-stop to post-stop differences in sPCDAI or PUCAI and laboratory markers between study groups (and subgroups). All combination regimens were analyzed independently. Chi-square and Kruskal–Wallis tests were used for comparisons between patients who did and did not require post-stop escalation. Hypothesis testing was conducted at an alpha of 0.05. All statistical analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC).

3 | RESULTS

3.1 | Study population

This study included 152 children with IBD (126 CD, 19 UC, 7 IBD-U) diagnosed at a median age of 12.9 (interquartile range [IQR] 10.8–15.5) years. At NCH, 6MP/AZA was more commonly prescribed for female patients (97% female) and MTX for male patients (96% male) due to differing side effect profiles by biological sex. The median patient age at initiation of

combination therapy was 13.7 (IQR 11.7–16.5) years, and the median duration of treatment with combination therapy at the time of IMM withdrawal was 1.7 years (IQR 1.1–2.7) (Table 1).

3.2 | Disease activity and markers of inflammation

IMM withdrawal had no significant effect on disease activity for patients with CD based on sPCDAI or patients with UC/IBD-U based on PUCAI regardless of disease phenotype, anti-TNF therapy, and IMM after IMM withdrawal (Figures 1A and 2A; $p > 0.05$). Among the 88 patients with IBD who were in clinical remission at the time of IMM withdrawal and had repeat sPCDAI or PUCAI scores post-stop, 25 patients (32%) experienced a clinical relapse (21 CD and 4 UC/IBD-U).

For patients with CD on IFX who discontinued the IMM ($n = 79$), there were significant increases in mean ESR, CRP, and Hgb (pre-stop vs. post-stop; Figure 1B–D; $p < 0.05$). These changes were seen in patients who discontinued MTX ($n = 47$), but not in patients who discontinued 6MP/AZA ($n = 32$). Notably, 45 out of the 47 patients with CD on IFX who discontinued MTX were male due to sex-based stratification of IMM therapy. Patients with CD on adalimumab who discontinued the IMM experienced a significant increase only in Hgb (pre-stop vs. post-stop; Figure 1D: $p < 0.05$).

In patients with UC/IBD-U on IFX, IMM withdrawal did not have a significant impact on ESR, CRP, or Alb (Figure 2B,C,E). IMM withdrawal led to a significant decrease in Hgb (pre-stop vs. post-stop; Figure 1D: $p < 0.05$), though only among patients who discontinued 6MP/AZA rather than MTX. Thirteen of the 14 patients with UC/IBD-U on IFX who discontinued 6MP/AZA were female due to sex-based IMM therapy.

In total, 28% ($n = 43$) of patients had a calprotectin level available before IMM withdrawal with a median value of 79 µg/g (IQR 30–294). After IMM withdrawal, 26% ($n = 39$) of patients had a repeat calprotectin level with a median of 122 µg/g (IQR 44–351), which was not significantly different for both patients with CD and UC/IBD-U. Pre-stop versus post-stop subgroup analyses were not completed because they lacked statistical power due to small sample sizes.

3.3 | Anti-TNF drug levels and antibodies

IMM withdrawal did not significantly impact anti-TNF drug levels regardless of disease phenotype, anti-TNF, or IMM. Pre-stop, patients with CD on IFX had mean IFX levels of 14.75 µg/mL (95% CI: 11.7–17.8) versus 12.32 µg/mL (95% CI: 9.4–15.2) post-stop (Figure 1F; $p > 0.05$). Patients with CD on adalimumab experienced a similar trend in drug levels, which decreased from a mean of 14.27 µg/mL (95% CI: 95% CI: 12.1–16.4) pre-stop to 12.93 µg/mL (95% CI: 10.9–14.9) post-stop (Figure 1F; $p > 0.05$). Lastly, for patients with UC/IBD-U, mean pre-stop IFX levels were 18.21 µg/mL (95% CI: 13.0–23.4) versus 13.21 µg/mL (95% CI: 8.0–18.4) post-stop (Figure 2F; $p > 0.05$).

Three patients (2%) developed IFX antibodies and undetectable IFX levels following IMM withdrawal. None of the patients on adalimumab who discontinued the IMM ($n = 47$) developed ADA. The first patient, a female with UC, developed antibodies (1:139) to IFX 8 months after 6MP was withdrawn. Before IMM withdrawal, she had been receiving IFX 10 mg/kg every 7 weeks and had an IFX trough level of 14.73 µg/mL. After detecting ADA, the physician restarted 6MP without an IFX dose or interval change. Repeat IFX levels were still undetectable with ADA, which prompted a switch from infliximab to adalimumab + 6 MP combination therapy to which she responded well. The second patient, a female with CD, developed ADA (1:31) to IFX around 12 months after AZA was withdrawn. In response, her infliximab dose was increased from 5 mg/kg every 6 weeks to 10 mg/kg every 6 weeks. The patient achieved sustained therapeutic anti-TNF levels and ADA was subsequently undetectable. The third patient, a male with CD, began experiencing increasing symptoms and developed ADA (1:606) to IFX at 8 months after MTX withdrawal. Before IMM withdrawal, this patient had been receiving IFX 10 mg/kg every 8 weeks, and he had trough levels of 4.49 µg/mL and endoscopic findings suggestive of deep remission. After detecting ADA, the patient began MTX monotherapy due to family preference and was noted to be in clinical remission on this therapy.

3.4 | Escalation of therapy

Of the 27 patients (18%; 23 CD + 4 UC/IBD-U) who required a post-stop escalation of therapy, 19 (70%) patients required escalation due to low anti-TNF levels (≤ 5 µg/mL for IFX and ≤7.5 µg/mL for adalimumab), five (19%) due to worsening of disease, and three (11%) due to ADA. Decisions to escalate therapy were based on the discretion of the provider. The median time to physician-directed escalation of therapy was 22.6 weeks (IQR 15–39). Twenty-two of the 27 patients (81%) requiring a poststop escalation of therapy had increases in anti-TNF dosage or frequency. Of the remaining five patients, two restarted the IMM, one changed anti-TNF medications and restarted the IMM, another stopped their anti-TNF medication and restarted the IMM, and one changed anti-TNF medications.

Only one of the five patients who required post-stop escalation due to worsening of disease recaptured

TABLE 1 Demographics of patients by diagnosis.

	Total (*N* = 152)	CD (*N* = 126)	UC/IBD-U (*N* = 26)
Age of diagnosis (yrs), med (IQR)	12.9 (10.8–15.5)	12.7 (12.4–15.0)	14.4 (11.4–16.4)
Age of first anti-TNF dose (yrs), med (IQR)	13.7 (11.7–16.4)	13.6 (11.7–15.9)	15.6 (13.0–17.1)
Combo duration (yrs), med (IQR)	1.7 (1.1–2.7)	1.7 (1.1–2.6)	2.3 (1.1–3.2)
Sex			
Female	73 (48.0%)	59 (46.8%)	14 (53.8%)
Anti-TNF			
Adalimumab	47 (30.9%)	47 (37.3%)	0 (0.0%)
IFX	105 (69.1%)	79 (62.7%)	26 (100.0%)
Immunomodulator			
6MP/AZA	72 (47.4%)	58 (46.0%)	14 (54.0%)
MTX	80 (52.6%)	68 (54.0%)	12 (46.0%)
Combination regimen			
IFX + 6MP/AZA	46 (29.7%)	32 (25.4%)	14 (53.8%)
IFX + MTX	59 (38.0%)	47 (37.3%)	12 (46.2%)
Adalimumab + 6MP/AZA	26 (16.8%)	26 (20.6%)	0
Adalimumab + MTX	21 (13.5%)	21 (16.7%)	0
sPCDAI			
Remission	–	18 (22.2%)	–
Mild	–	43 (53.1%)	–
Moderate/severe	–	20 (24.7%)	–
PUCAI			
Remission	–	–	1 (5.8%)
Mild	–	–	8 (47.1%)
Moderate/severe	–	–	8 (47.1%)
Disease location			
L1	–	13 (10.3%)	–
L2	–	19 (15.1%)	–
L3	–	93 (73.8%)	–
L4	–	1 (0.7%)	–
Disease behavior			
B1	–	103 (81.7%)	–
B2	–	7 (5.6%)	–
B3	–	11 (8.7%)	–
B2/B3	–	5 (4.0%)	–

(Continues)

TABLE 1 (Continued)

	Total ($N = 152$)	CD ($N = 126$)	UC/IBD-U ($N = 26$)
Perianal involvement	–	20 (15.9%)	–
Disease extension			
E1	–	–	0 (0.0%)
E2	–	–	3 (11.5%)
E3	–	–	8 (30.8%)
E4	–	–	15 (57.7%)

Abbreviations: 6MP/AZA, 6-mercaptopurine/azathioprine; CD, Crohn's disease; IBD-U, inflammatory bowel disease-unclassified; IFX, infliximab; IQR, interquartile range; med, median; MTX, methotrexate; PUCAI, pediatric ulcerative colitis activity index; sPCDAI, short pediatric CD activity index; UC, ulcerative colitis; yrs, years.

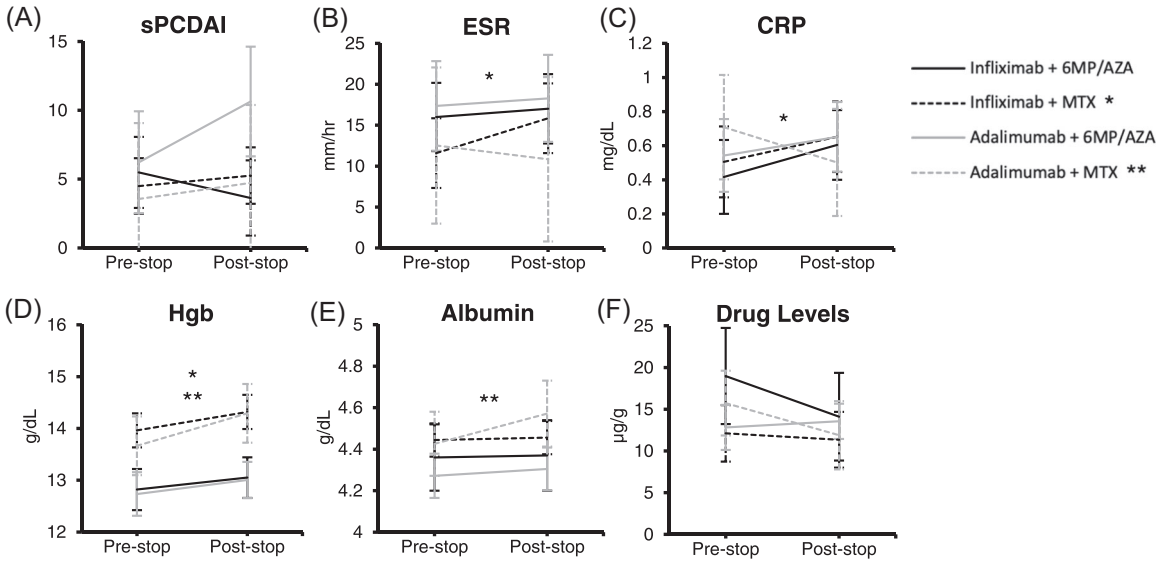


FIGURE 1 Disease activity and laboratory values of patients with CD following IMM withdrawal. (A) sPCDAI levels of disease activity did not differ significantly in patients with CD who discontinued the IMM. (B and C). Only patients that stopped the MTX while on IFX significantly increased serum inflammatory markers (ESR and CRP). (D and E) Hgb and albumin significantly increased in patients that stopped MTX while on adalimumab. (F) IMM withdrawal did not impact IFX and adalimumab levels. All combination regimens were analyzed independently of each other. 6MP, 6-mercaptopurine; AZA, azathioprine; CD, Crohn's disease; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; Hgb, Hemoglobin; IFX, infliximab; IMM, immunomodulator; MTX, methotrexate; sPCDAI, short pediatric CD activity index.

remission following the initial intervention, which was an increase in adalimumab from biweekly to weekly injections. Of the remaining four patients whose disease worsened, all four failed to recapture remission following their initial escalations of therapy, which included increasing their anti-TNF dose or frequency ($n = 2$), restarting the IMM ($n = 1$), and switching from adalimumab to ustekinumab ($n = 1$). After these initial interventions, all four patients eventually switched to new biologic medications and one required an ileocecectomy before recapturing remission.

In contrast to the 27 patients (18%) who required a post-stop escalation of therapy, 12 patients (8%) had provider-directed decreases in anti-TNF dose or frequency after noting high anti-TNF levels. Before IMM withdrawal, 6 of these patients had anti-TNF levels available, and all levels were >20 µg/mL.

3.5 | Factors contributing to post-stop escalations of therapy

Patients requiring post-stop escalation had a significantly higher pre-stop median ESR compared to patients who did not require escalation (Table 2; $p < 0.05$). The difference in pre-stop CRP between patients requiring post-stop escalation group and patients not requiring post-stop escalation was statistically significant despite identical median levels before IMM withdrawal (Table 2; $p < 0.05$). The statistical significance of this difference was driven by the distribution of patients who had a CRP of greater than 0.4 mg/dL, which was 26.9% of patients requiring post-stop escalation compared to only 7.9% of patients not requiring post-stop escalation. While pre-stop inflammatory markers ESR and CRP were significant

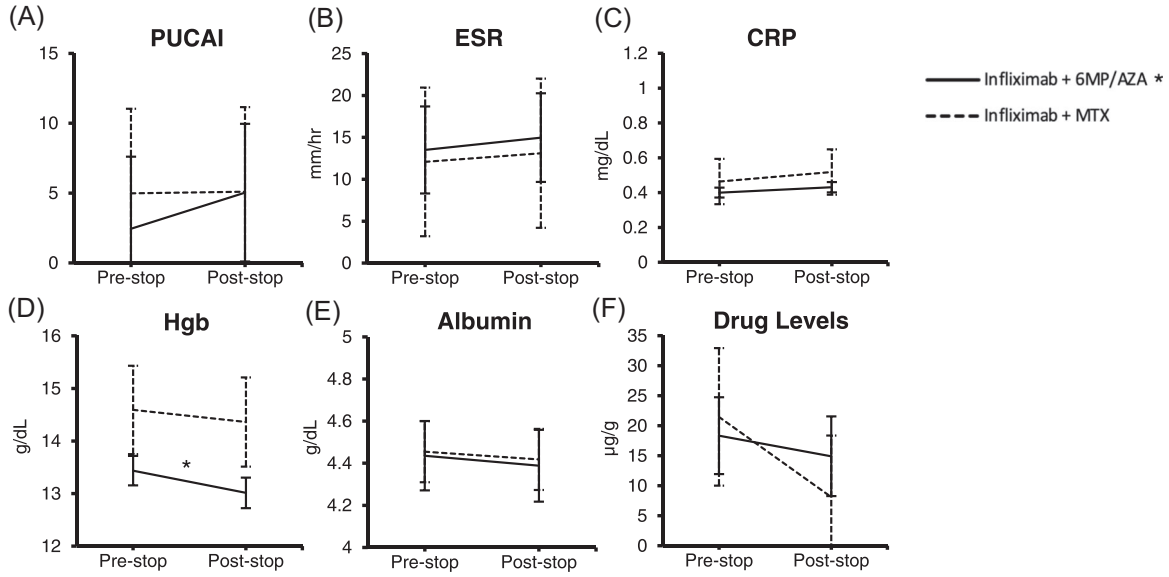


FIGURE 2 Disease activity and laboratory values of patients with UC/IBD-U following IMM withdrawal. (A) IMM withdrawal did not significantly impact disease activity scores (PUCAI). (B–C). IMM withdrawal did not significantly impact inflammatory markers (ESR and CRP). (D) IMM withdrawal significantly decreased Hgb levels in patients that stopped 6MP/AZA. (E) IMM withdrawal did not significantly impact albumin. (F) IMM withdrawal did not significantly impact infliximab levels. All combination regimens were analyzed independently of each other. 6MP/AZA, 6-mercaptopurine/azathioprine; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; Hgb, Hemoglobin; IMM, immunomodulator; MTX, methotrexate; PUCAI, pediatric ulcerative colitis activity index; UC/IBD-U, ulcerative colitis/inflammatory bowel disease-unspecified.

between the groups, pre-stop calprotectins and clinical disease activity scores were not significantly different. IFX and adalimumab levels before IMM withdrawal were significantly lower in patients who required post-stop escalation of therapy compared to those who did not (Table 2; $p < 0.05$).

4 | DISCUSSION

Anti-TNF medications have largely become first-line medications for the treatment of IBD in both adults and children.[24] Adult studies such as SONIC[5] and SUCCESS[25] found that combination therapy, which consists of both an anti-TNF agent and an IMM, is superior at treating IBD compared to monotherapy, although these studies did not include therapeutic drug monitoring or anti-TNF dose adjustments. In pediatrics, data on combination therapy is generally mixed. For example, a 2015 pediatric randomized controlled trial assessing the efficacy of combination therapy (IFX + AZA or MTX) compared to IFX monotherapy found similar results between the two groups.[26] In contrast, a 2023 pediatric randomized controlled trial comparing anti-TNF monotherapy to anti-TNF + MTX combination therapy in patients with CD found that patients on adalimumab-based combination therapy experienced half as many episodes of treatment failure compared to patients on adalimumab monotherapy.[10] Moreover, several pediatric retrospective studies have found distinct benefits of combination therapy in comparison to anti-TNF monotherapy in CD, such as higher rates of remission and greater duration of therapeutic response.[9,11,27]

The risks of combination therapy are well-defined and include bone marrow suppression, opportunistic infection, and lymphoma.[13,28] As a result, IMM withdrawal is common practice to mitigate IMM-related adverse events, especially in young patients with IBD for whom long-term combination therapy poses the greatest risks.[29] Yet, pediatric studies assessing the impacts of IMM withdrawal from anti-TNF combination therapy are limited.

We found among all comparisons of disease phenotype (CD, UC/IBD-U), anti-TNF agent (IFX, adalimumab), and IMM (6MP/AZA, MTX), patients with CD on IFX who discontinued MTX saw a significant increase in serum inflammatory markers (ESR and CRP) but not in disease activity or drug levels. In contrast, patients with CD and UC/IBD-U on IFX + 6MP/AZA and patients with CD on adalimumab who discontinued the IMM did not have a significant change in serum inflammatory markers, disease activity, or drug levels.

While disease activity did not worsen after IMM withdrawal, we found that 18% of patients required a post-stop escalation of therapy, most commonly due to subtherapeutic anti-TNF levels ($n = 19$) rather than symptoms ($n = 5$). Several factors were identified that may predict whether a patient would require post-stop escalation, including low anti-TNF drug levels and high

TABLE 2 Pre-stop factors contributing to escalation versus no escalation.

	Escalation ($n = 27$)	No escalation ($n = 125$)	p
Sex			0. 99
Male	14 (18%)	65 (82%)	
Female	13 (18%)	60 (82%)	
Diagnosis			0. 73
CD	23 (18%)	103 (82%)	
UC/IC	4 (15%)	22 (85%)	
Anti-TNF			0.045
Infliximab	23 (85%)	82 (66%)	
Adalimumab	4 (15%)	43 (34%)	
Immunomodulator			0. 45
6MP/AZA	11 (41%)	61 (49%)	
MTX	17 (59%)	64 (51%)	
Demographics, med (IQR)			
Age at diagnosis (yrs)	11.55 (8.9–14.7)	13.19 (11.0–15.5)	0. 12
Age starting combo (yrs)	12.99 (11.2–16.9)	14.25 (12.0–16.3)	0. 31
Combo length (yrs)	2 (0.9–2.9)	1.7 (1.2–2.6)	0. 85
Disease activity, med (IQR)			
sPCDAI	0 (0–10)	0 (0–10)	0. 11
PUCAI	5 (3.75–6.25)	0 (0–5)	0. 49
Laboratory values, med (IQR)			
IFX level (μg/mL)	9.9 (5.4–13.2)	15.39 (10.0–21.2)	**0. 01**
Adalimumab level (μg/mL)	7.81 (6.8–9.8)	13.42 (11.4–17.7)	**0. 04**
Fecal calprotectin (μg/g)	146.5 (26–288)	71 (31.5–270)	0. 67
ESR (mm/h)	14 (9–27)	9.5 (4–16)	**0. 01**
CRP (mg/dL)	0.4 (0.4–0.48)	0.4 (0.4–0.4)	**0. 01**
Albumin (g/dL)	4.4 (4.3 – 4.6)	4.4 (4.2–4.6)	0. 33
Hemoglobin (g/dL)	13.5 (12.8–13.9)	13.6 (12.7–14.2)	0. 65

Abbreviations: 6MP/AZA: 6-mercaptopurine/azathioprine; CD: Crohn's disease; CRP: C-reactive protein; Combo: combination therapy; ESR: erythrocyte sedimentation rate; IFX: infliximab; IQR: interquartile range; med: median; MTX: methotrexate; PUCAI, pediatric ulcerative colitis activity index; sPCDAI, short pediatric Crohn's disease activity index; TNF, tumor necrosis factor; UC: ulcerative colitis; yrs: years.

serum inflammatory markers (ESR and CRP) before IMM withdrawal. IFX levels less than 10 mcg/mL, adalimumab level less than 7.8 mcg/mL, ESR greater than 14 mm/h, and CRP greater than 0.4 mg/dL before discontinuing the IMM may be predictors of a sub-optimal response to IMM withdrawal. Disease type and choice of IMM did not differ significantly between groups, but choice of anti-TNF did with 22% of patients on IFX ($n = 105$) requiring a post-stop escalation of therapy compared to 9% for adalimumab ($n = 47$).

We are currently aware of only one retrospective study investigating IMM withdrawal in pediatric patients with IBD, which found that only 10.5% of patients experienced clinical relapse in a median of 12 months following IMM withdrawal.[30] Comparing patients who relapsed after IMM withdrawal versus patients who did not, there were no differences for all examined variables. This study did not assess whether IMM withdrawal impacted inflammatory markers or drug levels.

There have been multiple adult studies evaluating the impacts of IMM withdrawal. A recent systematic review and meta-analysis included eight randomized controlled trials comparing IMM or anti-TNF withdrawal versus continued combination therapy in adult patients with IBD.[17] The study found no difference in risk of

relapse among patients who discontinued the IMM versus patients who continued combination therapy, but the evidence was of low certainty. Conversely, patients who discontinued the anti-TNF had a 2.4-times greater risk of relapse compared to patients continuing combination therapy. Included in this meta-analysis, the SPARE trial, an open-label randomized controlled trial of adult patients with CD, found that discontinuing the IMM led to clinical relapse in 12% of patients versus 9% among patients who did not discontinue the IMM.[18] Young age (<17 years old) at diagnosis was associated with an increased risk of relapse following IMM withdrawal.

In a retrospective adult study from Mahmoud et al., patients on combination therapy who discontinued the IMM were compared to patients who remained on combination therapy.[16] They concluded that IMM withdrawal did not put patients at increased risk of loss of response compared to patients continuing on combination therapy, though there was a high incidence of ADA (10.3%) in the IMM withdrawal group and 18% of patients required dose escalations during a median follow up period of 1.7 years. Our study found similar rates of escalation in pediatric patients following IMM withdrawal though over a shorter follow-up period. Additionally, there were fewer instances of ADA (1.9%) compared to in the adult study.

Our study has several limitations. As a retrospective cohort analysis, the study may have been subject to confounding variables beyond our ability to control. Our analysis was also limited by missing data. For example, fecal calprotectin and anti-TNF drug levels are not routinely collected by all providers. Another important limiting factor of our analysis is the lack of a control group of patients continuing combination therapy. Additionally, because of historical sex-based stratification practices at NCH, 97% patients who discontinued 6MP/AZA were female, which limits the generalizability of our findings. Lastly, endoscopic data was not included because it was not a standard of care during the time frame of this study.

In conclusion, we found that IMM withdrawal from anti-TNF combination therapy to anti-TNF monotherapy may be considered safe in the setting of higher anti-TNF drug levels and normal serum inflammatory markers before IMM withdrawal. Our findings align well with the most recent update to the IBD management guidelines from the ESPGHAN, which recommends consideration of IMM withdrawal after 6–12 months of combination therapy, but only if anti-TNF levels are within therapeutic range (IFX ≥ 5 μg/mL; adalimumab ≥ 7.5 μg/mL) and disease activity is well-controlled.[31] Additionally, our findings suggest that reevaluating response to IMM withdrawal using both anti-TNF levels and inflammatory markers should be considered, especially in patients with CD on IFX who discontinue MTX. Ultimately, IMM withdrawal should be carefully considered at the joint discretion of the provider, patient, and family, within the framework of its risks and benefits.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

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