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Natural History of Pediatric Patients With Crohn's Disease Treated With Mesalamine Therapy

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ABSTRACT

Background: 5-aminosalicylates (5-ASA) are used to treat mild to moderate ulcerative colitis. Despite their lack of efficacy in Crohn disease (CD), they are still used in real-world practice. Additionally, when patients have progressive disease, they may escalate to biologic therapy, at which time 5-ASA may or may not be discontinued.

Objectives: The aim of this study is to assess the clinical outcomes of patients started on 5-ASA for the treatment of pediatric CD. The secondary aims were to evaluate the outcomes of those who continue 5-ASA to those who discontinue 5-ASA upon biologic escalation.

Methods: We performed a single-center retrospective chart review of pediatric CD patients from 2010 to 2019 who were initially treated with 5-ASA. Demographics, medication and laboratory data, and clinical disease activity were collected.

Results: Sixty-one patients were included in the study; the majority had inflammatory CD with ileocolonic involvement. Twenty-four patients were on a concomitant immunomodulator. The majority of patients (85.2%) required escalation to biologics. Thirty-two patients (61.5%) who escalated to biologic therapy continued on 5-ASA. Eighty percent of patients achieved clinical remission at 1 year, and there was no difference between those who continued 5-ASA at time of biologic initiation compared to those who did not continue the medication. Patients who discontinued 5-ASA had an average annual cost savings of $6741.

Conclusion: 5-ASA is not a durable monotherapy for the treatment of pediatric CD. Patients who require escalation from 5-ASA to biologic therapy do not benefit from concomitant 5-ASA therapy. Further prospective studies are needed to confirm these findings.

Key Words: pediatrics, Crohn disease, biologics, anti-TNFα, mesalamine, 5-ASA

What Is Known

- Although 5-aminosalicylates (5-ASA) is not recommended for the treatment of pediatric Crohn disease, it is still used in real-world practice.
- Discontinuation of 5-ASA in adult inflammatory bowel disease patients who escalate to biologic therapy is not associated with an increase in adverse outcomes.

What Is New

- 5-ASA is not a durable therapy for the treatment of pediatric Crohn disease.
- Discontinuation of 5-ASA when escalating to biologic therapy is not associated with worse outcomes in pediatric inflammatory bowel disease.
- There are potential cost savings for patients who discontinue 5-ASA after starting biologics.

INTRODUCTION

Crohn's disease (CD) is a chronic inflammatory disorder of the gastrointestinal tract characterized by alternating periods of relapse and remission. Characteristics of CD include skip lesions, perianal and fistulizing disease, and involvement of the small intestine and upper gastrointestinal tract. Approximately 10% of CD patients are diagnosed in the pediatric period (1). The treatment paradigm of inflammatory bowel disease (IBD) has shifted from addressing clinical symptoms alone to achieving endoscopic remission (2,3). Various medication classes are available to treat pediatric CD, and the choice of therapy depends on the clinical presentation and severity of the disease at time of diagnosis.

The mechanism of 5-aminosalicylates (5-ASA) is unclear, but is thought to exert anti-inflammatory effects on the cyclooxygenase and lipoxygenase pathways and decrease the formation of prostaglandins and leukotrienes (4). There are multiple formulations, each with varying degrees of systemic absorption and different sites of drug release. 5-ASA medications are primarily used for induction and maintenance of remission in mild to moderate ulcerative colitis (UC). The use of 5-ASA has not shown to be beneficial in the induction and maintenance of remission in CD (5,6). Despite the current absence of recommendations for their use, 5-ASA medications are commonly prescribed in real-world practice, especially for patients with mild CD (7–9). This was especially common with the practice of "step-up" therapy, where patients escalated to an immunomodulator or biologic after medication failure. In addition, for those patients who start on 5-ASA and escalate to biologics, there is a subset who remain on 5-ASA therapy. Recent adult studies have shown there is no additional benefit and no increase in adverse outcomes for

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patients with IBD who remain on 5-ASA after escalation to biologic therapy (7,10–13).

The primary aim of our study was to assess the clinical outcomes of patients who were started on 5-ASA for the treatment of pediatric CD. The secondary aims were to evaluate the outcomes of those who continue 5-ASA to those who discontinue 5-ASA upon escalation to biologic therapy.

METHODS

Study Design

We performed a single-center retrospective chart review of pediatric IBD patients who were seen by the Division of Pediatric Gastroenterology, Hepatology, and Nutrition at Rainbow Babies and Children's Hospital, in Cleveland, OH, from 2010 to 2019. Patients were identified from a locally maintained database for pediatric patients with IBD. Data collected included demographics and disease classification. Medications, laboratory data, and clinical disease activity were collected at time of IBD diagnosis, and at 3 and 6-month intervals for the following year after biologic escalation, or for the first year on 5-ASA therapy if they did not step up to biologic therapy. Medical visits were reviewed to assess disease activity using the short Pediatric Crohn Disease Activity Index (sPCDAI) (14). Documented symptoms were scored according to the sPCDAI. If symptoms were not noted, the assumption was the patient was asymptomatic in that category.

Participants

Inclusion criteria were: (1) patients seen by the Division of Pediatric Gastroenterology, Hepatology, and Nutrition at Rainbow Babies and Children's Hospital from 2010 to 2019, who were diagnosed between 7 and 18 years of age, (2) with diagnosis of CD, and (3) started on 5-ASA therapy. Patients who required escalation to infliximab or adalimumab must have remained on the same biologic therapy for at least 1 year. Patients were excluded if they were below 7 years of age or above 18 years of age at diagnosis, or had diagnosis of UC or IBD-unclassified. A patient was defined as having discontinued 5-ASA therapy if it was no longer prescribed within 90 days of escalating to biologics.

Statistical Analysis

For the descriptive statistics, demographics were described using frequency and percentages for categorical variables, as appropriate. Categorical variables were analyzed with the χ^2 test or Fisher exact test. Paired analysis on the clinical characteristics and laboratory results was performed. The paired analysis on the categorical variables was performed using Cochran's Q test and repeated measures ANOVA on the continuous variables. $P < 0.05$ was considered statistically significant for the analysis. All the analysis was performed using SAS software, version 9.4 (SAS Institute, Cary, NC).

Ethical Considerations

This study was approved by the Institutional Review Board at University Hospitals, in Cleveland, OH (IRB Study Number 20201255).

RESULTS

Baseline Characteristics

Patient demographics and disease characteristics are presented in Table 1. A total of 61 patients were included in the study and classified using the Paris classification (15) (Supplemental Digital Content Figure 1, http://links.lww.com/PG9/A139). The majority of patients were Caucasian (82%) and male (64%). Most patients were diagnosed between 10 and 16 years of age, with mean age of 12.55 years, and had inflammatory CD with ileocolonic involvement. Fifty-one percent of patients had upper gastrointestinal involvement and 21% had perianal disease at diagnosis. The majority of patients (71%) had moderate to severe disease at diagnosis, as defined by sPCDAI. Three patients were noted to have sPCDAI scores that correlated to quiescent symptoms

TABLE 1. Patient characteristics at baseline and 1 year

	Patients N = 61*
Sex (Female)	22 (36%)
Ethnicity	
Caucasian	50 (82%)
African American	9 (15%)
Middle Eastern	2 (3%)
Mean age at diagnosis, in years	12.55 (9.93, 14.26)
Age	
A1a (0 – <10 year)	17 (28%)
A1b (10 – <17)	41 (67%)
A2 (17–40)	3 (4.9%)
Disease location and behavior	
L1: Terminal ileum	10 (16%)
L2: Colonic	9 (15%)
L3: Ileocolonic	42 (69%)
L4a: Upper proximal GI tract	31 (51%)
L4b: Upper and distal upper GI tract	2 (3.3%)
B1: Inflammatory	53 (87%)
B2: Stricturing	6 (9.8%)
B3: Penetrating	1 (1.6%)
B2B3: Stricturing, penetrating	1 (1.6%)
P: Perianal	13 (21%)
Clinical activity (sPCDAI) at diagnosis	
Remission	3 (4.9%)
Mild	15 (25%)
Moderate	18 (30%)
Severe	25 (41%)
Laboratory values at diagnosis	
C-reactive protein	1.69 (0.70, 5.25)
Hemoglobin	10.80 (9.90, 11.90)
Albumin	3.10 (2.62, 3.50)
Clinical activity (sPCDAI) at 1 year	
Remission (<12.5)	48 (80%)
Mild (12.5–40)	10 (17%)
Moderate (40.5–57.5)	1 (1.7%)
Severe (>57.5)	1 (1.7%)
Unknown	1
Laboratory values at 1 year	
C-reactive protein	0.30 (0.30, 0.56)
Hemoglobin	13.00 (12.00, 14.12)
Albumin	4.10 (3.80, 4.30)

GI = gastroenterology; sPCDAI = short Pediatric Crohn Disease Activity Index.
*N (%); median (IQR).

at diagnosis, but in the individual symptom assessment, did report symptoms such as abdominal pain, small quantity of hematochezia or diarrhea, and/or had 1 abnormal lab. Twenty-four patients (39.3%) were started on an immunomodulator in conjunction with a 5-ASA at time of diagnosis and all of them were on azathioprine. None of the patients were started on exclusive enteral nutrition for induction. We performed a subanalysis (Table 2) that showed these patients were younger (mean age 11.84 vs 12.85 years, $P = 0.031$) and had higher C-reactive protein (CRP) at diagnosis ($P = 0.004$). Otherwise, there were no statistically significant differences observed in the baseline characteristics between those 2 groups.

Biologic Escalation

Fifty-two patients (85.2%) required escalation to biologics. The mean age at time of biologic initiation was 14.02 years, with a disease duration of 1.3 years (Table 3). When comparing

TABLE 2. Comparison of 5-ASA monotherapy and concomitant immunomodulator therapy at diagnosis and 1 year

	5-ASA monotherapy N = 37*	5-ASA + immunomodulator N = 24*	*P* value†
Sex (Female)	15 (41%)	7 (29%)	0.366
Ethnicity			0.543
Caucasian	29 (78%)	21 (88%)	
African American	7 (19%)	2 (8.3%)	
Middle Eastern	1 (3%)	1 (4.2%)	
Mean age at diagnosis, in years	12.85 (10.81, 14.63)	11.84 (8.90, 12.65)	0.031
Age			0.142
A1a (0 – <10 year)	7 (19%)	10 (42%)	
A1b (10 – <17)	28 (76%)	13 (54%)	
A2 (17–40)	2 (5.4%)	1 (4.2%)	
Disease location and behavior			
L1: Terminal ileum	5 (14%)	5 (21%)	0.495
L2: Colonic	5 (14%)	4 (17%)	0.729
L3: Ileocolonic	27 (73%)	15 (62%)	0.388
L4a: Upper proximal GI tract	22 (59%)	9 (38%)	0.094
L4b: Upper and distal upper GI tract	2 (5.4%)	0 (0%)	0.515
B1: Inflammatory	33 (89%)	20 (83%)	0.7
B2: Stricturing	4 (11%)	2 (8.3%)	>0.999
B3: Penetrating	0 (0%)	1 (4.2%)	0.393
B2B3: Stricturing, penetrating	0 (0%)	1 (4.2%)	0.393
P: Perianal	9 (24%)	4 (17%)	0.476
Clinical activity (sPCDAI) at diagnosis			0.929
Remission	2 (5.4%)	1 (4.2%)	
Mild	10 (27%)	5 (21%)	
Moderate	11 (30%)	7 (29%)	
Severe	14 (38%)	11 (46%)	
Laboratory values at diagnosis			
C-reactive protein	0.95 (0.50, 2.64)	3.99 (1.30, 7.35)	0.004
Hemoglobin	11.00 (10.35, 12.35)	10.70 (9.50, 11.17)	0.117
Albumin	3.40 (2.70, 3.55)	2.90 (2.65, 3.15)	0.111
Clinical activity (sPCDAI) at 1 year			0.732
Remission (<12.5)	30 (81%)	18 (78%)	
Mild (12.5–40)	6 (16%)	4 (17%)	
Moderate (40.5–57.5)	0 (0%)	1 (4.3%)	
Severe (>57.5)	1 (2.7%)	0 (0%)	
Laboratory values at 1 year			
C-reactive protein	0.30 (0.30, 0.69)	0.30 (0.30, 0.30)	0.184
Hemoglobin	12.95 (12.23, 14.30)	13.00 (12.00, 13.38)	0.386
Albumin	4.15 (3.88, 4.40)	4.10 (3.80, 4.20)	0.258

5-ASA = 5-aminosalicylates; GI = gastroenterology; sPCDAI = short Pediatric Crohn Disease Activity Index.
*N (%); median (IQR).
†Pearson's χ^2 test; Fisher exact test; Wilcoxon rank sum test.

TABLE 3. Characteristics of patients who escalated to biologic therapy at baseline and 1 year

	Overall N = 52*	5-ASA monotherapy N = 35*	5-ASA + immunomodulator N = 17*	*P* value†
Mean age at time of biologic escalation, in years	14.02 (12.61, 15.84)	14.67 (12.84, 17.15)	13.75 (11.93, 14.84)	0.048
Disease duration, in years	1.30 (0.82, 2.32)	1.58 (0.84, 2.50)	1.27 (0.71, 1.86)	0.169
Clinical activity (sPCDAI) at escalation				0.755
Remission	6 (12%)	3 (8.6%)	3 (18%)	
Mild	30 (58%)	20 (57%)	10 (59%)	
Moderate	10 (19%)	7 (20%)	3 (18%)	
Severe	6 (12%)	5 (14%)	1 (5.9%)	
Laboratory values at escalation				
C-reactive protein	0.86 (0.30, 2.95)	1.00 (0.33, 3.10)	0.62 (0.30, 2.35)	0.589
Hemoglobin	11.60 (10.50, 13.30)	11.50 (10.45, 13.40)	11.85 (10.57, 12.88)	0.935
Albumin	3.60 (3.18, 4.00)	3.60 (3.10, 4.00)	3.70 (3.50, 3.90)	0.417
Clinical activity (sPCDAI) at 1 year				0.48
Remission (<12.5)	40 (77%)	28 (80%)	12 (71%)	
Mild (12.5–40)	10 (19%)	6 (17%)	4 (24%)	
Moderate (40.5–57.5)	1 (1.9%)	0 (0%)	1 (5.9%)	
Severe (>57.5)	1 (1.9%)	1 (2.9%)	0 (0%)	
Laboratory values at 1 year				
C-reactive protein	0.30 (0.30, 0.60)	0.31 (0.30, 0.73)	0.30 (0.30, 0.32)	0.309
Hemoglobin	12.90 (12.00, 14.25)	12.90 (12.15, 14.30)	12.75 (11.95, 13.45)	0.405
Albumin	4.10 (3.80, 4.35)	4.20 (3.85, 4.40)	3.95 (3.68, 4.12)	0.058

5-ASA = 5-aminosalicylates; sPCDAI = short Pediatric Crohn Disease Activity Index.
*N (%); median (IQR).
†Pearson's χ^2 test; Fisher exact test; Wilcoxon rank sum test.

the 5-ASA monotherapy group with those on concomitant therapy, 94.6% escalated to biologic therapy versus 70.8%. Patients on an immunomodulator with 5-ASA were younger at time of biologic initiation ($P = 0.048$) (Table 3). Although more patients in the 5-ASA monotherapy group had moderate to severe disease activity scores at time of biologic escalation, there was no difference between the 2 groups in terms of their clinical symptom assessment ($P = 0.755$). In addition, there was no statistically significant difference with CRP ($P = 0.589$), albumin ($P = 0.417$), or hemoglobin ($P = 0.935$) between the 2 groups at time of biologic escalation.

There were 3 patients on 5-ASA monotherapy who were considered to be in clinical remission based on the sPCDAI score. However, it is important to note that these patients either still had symptoms such as abdominal pain, or abnormal labs at time of biologic escalation, but did not score high enough to differentiate between quiescent symptoms and mild symptoms. There were 2 patients on 5-ASA monotherapy who did not escalate to biologic therapy. Both of these patients had colonic CD with no upper gastroenterology or small bowel involvement. Thirty-two patients (61.5%) who escalated to biologic therapy continued on a 5-ASA.

Clinical Disease and Biochemical Activity Outcomes

Overall, 80% of patients achieved clinical remission at 1 year, as defined by sPCDAI (Table 1). There was no difference in sPCDAI activity score among patients who started on 5-ASA monotherapy and those on 5-ASA and an immunomodulator ($P = 0.732$). Of the patients started on biologic therapy, 77% were in clinical remission; 3.8% of patients had either moderate or severe disease at 1 year (Table 4). When evaluating patients who continued 5-ASA upon biologic initiation compared to those who discontinued the medication, there was no difference in the number of patients who achieved clinical remission at 1 year. This was seen in both the 5-ASA monotherapy group ($P = 0.128$) and the immunomodulator and 5-ASA combined group ($P = 0.145$) (Tables 4 and 5).

We recorded data for CRP, albumin, and hemoglobin to assess biochemical activity. Median values at time of biologic initiation and at 1 year are reported in Tables 2 and 3. When comparing median values for CRP, albumin, and hemoglobin at 1 year, it is noted that they were all within normal limits and no difference between those who were started on a 5-ASA and those who were started on a concomitant immunomodulator with 5-ASA. Similarly, there was no difference in CRP and hemoglobin among those who discontinued 5-ASA and those who continued 5-ASA upon biologic therapy, with the exception of the concomitant immunomodulator group, where the patients who discontinued 5-ASA at time of biologic initiation had higher median albumin at 1 year ($P = 0.033$). However, the median and IQR for those who continued and discontinued 5-ASA were still within the normal range (Tables 4 and 5).

Of the patients who did not escalate to biologic therapy and had a visit at 1 year, all were in clinical and biochemical remission.

Steroid Use

All patients in our study achieved steroid-free remission at 1 year. There were 23 patients who were started on systemic steroids at time of biologic escalation but were weaned off by 1 year. Similarly, none of the patients who remained on 5-ASA and did not escalate to biologic therapy were on systemic steroids at 1 year.

Costs of Care

The majority of our patients on 5-ASA were prescribed Pentasa (65.6%); other formulations prescribed included Apriso, Asacol, Colazol, Lialda, and sulfasalazine. Using average wholesale cost per year, the cost burden of 5-ASA therapy in our patient cohort who

TABLE 4. Comparison of patients who started on 5-ASA monotherapy and continued versus discontinued 5-ASA at biologic escalation

	Overall N = 35*	Remained on 5-ASA N = 19*	Discontinued 5-ASA N = 16*	*P* value†
Clinical activity (sPCDAI) at switch				0.952
Remission (<12.5)	3 (8.6%)	2 (11%)	1 (6.2%)	
Mild (12.5–40)	20 (57%)	11 (58%)	9 (56%)	
Moderate (40.5–57.5)	7 (20%)	3 (16%)	4 (25%)	
Severe (>57.5)	5 (14%)	3 (16%)	2 (12%)	
Laboratory values at escalation				
C-reactive protein	1.00 (0.33, 3.10)	0.80 (0.44, 3.51)	1.40 (0.30, 2.69)	0.855
Hemoglobin	11.50 (10.45, 13.40)	11.50 (10.40, 13.90)	11.55 (10.95, 13.00)	0.804
Albumin	3.60 (3.10, 4.00)	3.40 (3.10, 4.15)	3.60 (3.22, 4.00)	0.947
Clinical activity (sPCDAI) at 1 year				0.128
Remission (<12.5)	28 (80%)	13 (68%)	15 (94%)	
Mild (12.5–40)	6 (17%)	5 (26%)	1 (6.2%)	
Moderate (40.5–57.5)	0 (0%)	0 (0%)	0 (0%)	
Severe (>57.5)	1 (2.9%)	1 (5.3%)	0 (0%)	
Laboratory values at 1 year				
C-reactive protein	0.31 (0.30, 0.73)	0.36 (0.30, 0.61)	0.30 (0.10, 0.78)	0.301
Hemoglobin	12.90 (12.15, 14.30)	13.00 (11.90, 14.40)	12.85 (12.45, 13.85)	>0.999
Albumin	4.20 (3.85, 4.40)	4.00 (3.80, 4.40)	4.25 (3.98, 4.40)	0.444

5-ASA = 5-aminosalicylates; sPCDAI = short Pediatric Crohn Disease Activity Index.
*N (%); median (IQR).
†Pearson's χ^2 test; Fisher exact test; Wilcoxon rank sum test.

TABLE 5. Comparison of patients who started on concomitant immunmodulator and continued versus discontinued 5-ASA at biologic escalation

	Overall N = 17*	Remained on 5-ASA N = 13*	Discontinued 5-ASA N = 4*	*P* value†
Clinical activity (sPCDAI) at switch				0.439
Remission (<12.5)	3 (18%)	1 (7.7%)	2 (50%)	
Mild (12.5–40)	10 (59%)	8 (62%)	2 (50%)	
Moderate (40.5–57.5)	3 (18%)	3 (23%)	0 (0%)	
Severe (>57.5)	1 (5.9%)	1 (7.7%)	0 (0%)	
Laboratory values at escalation				
C-reactive protein	0.62 (0.30, 2.35)	0.62 (0.30, 2.35)	0.99 (0.41, 2.99)	0.854
Hemoglobin	11.85 (10.57, 12.88)	11.65 (10.55, 12.50)	12.55 (11.62, 13.15)	0.504
Albumin	3.70 (3.50, 3.90)	3.60 (3.20, 3.80)	3.95 (3.88, 4.08)	0.061
Clinical activity (sPCDAI) at 1 year				0.145
Remission (<12.5)	12 (71%)	9 (69%)	3 (75%)	
Mild (12.5–40)	4 (24%)	4 (31%)	0 (0%)	
Moderate (40.5–57.5)	1 (5.9%)	0 (0%)	1 (25%)	
Severe (>57.5)	0 (0%)	0 (0%)	0 (0%)	
Laboratory values at 1 year				
C-reactive protein	0.30 (0.30, 0.32)	0.30 (0.30, 0.38)	0.24 (0.16, 0.30)	0.082
Hemoglobin	12.75 (11.95, 13.45)	12.35 (11.95, 13.12)	14.25 (13.40, 14.60)	0.202
Albumin	3.95 (3.68, 4.12)	3.80 (3.58, 4.10)	4.20 (4.12, 4.28)	0.033

5-ASA = 5-aminosalicylates; sPCDAI = short Pediatric Crohn Disease Activity Index.
*N (%); median (IQR).
†Pearson's χ^2 test; Fisher exact test; Wilcoxon rank sum test.

continued 5-ASA therapy was estimated to be $215 715, or an average of $6741 per patient, per year.

DISCUSSION

To our knowledge, this is the first pediatric study to evaluate the clinical outcomes of pediatric patients with CD who were started on 5-ASA as initial treatment. We found the majority of patients in our cohort required escalation to biologic therapy. Further analysis showed that all but 2 patients on 5-ASA monotherapy escalated to infliximab or adalimumab compared to 70.8% of those who were on an immunomodulator with 5-ASA. The majority of patients achieved clinical remission at 1 year. Additionally, there was no difference in clinical remission as defined by sPCDAI among those who continued or discontinued 5-ASA upon escalation to biologic therapy. We did find that those who discontinued 5-ASA at time of biologic initiation had higher albumin at 1 year, but the median albumin between both groups were within normal limits. Median CRP, hemoglobin, and erythrocyte sedimentation rate were also within normal limits, with no statistically significant difference between the different patient cohorts.

5-ASA therapies are used to treat mild to moderate IBD, typically UC, and in some instances, CD of the colon. While previous studies may have shown some benefit of 5-ASA in the treatment of CD (16), this class of medications is currently not recommended as therapy for patients with CD (1). Despite this, 5-ASA medications may still be used in clinical practice, especially those with mild clinical and endoscopic disease (8,9). In our study, we evaluated a subset of patients who had mild disease as defined by the sPCDAI and without perianal involvement; the majority (83.3%) still escalated to biologic therapy. The 2 patients who did not require biologic escalation had isolated colonic disease with mild symptoms and normal labs. Based on our results, it may be reasonable to consider 5-ASA medications for mild CD of the colon only. Because we did not include patients 6 years and under in our study, our results may not be generalizable to patients with very early onset IBD.

In addition, we conducted an analysis comparing patients on ASA monotherapy to those on ASA with concomitant immunomodulator therapy. We found that 94.6% of patients on monotherapy escalated to biologic compared to 70.8% of patients on 5-ASA in combination with an immunomodulator. Fewer patients on concomitant immunomodulator therapy escalated to biologic likely due to the effect of the immunomodulator. This further illustrates that 5-ASA is not a durable therapy for the treatment of CD, especially if the patient has moderate to severe disease. In such patients, starting biologic therapy early may result in better clinical outcomes (17).

For patients who escalate to biologic therapy, the decision remains whether prior medications should be continued. In regards to 5-ASA medications, adult studies have shown there is no benefit or increased risk of adverse events in patients who discontinue 5-ASA upon biologic therapy initiation (7,10–13). A pooled analysis of individual participant data from clinical trials showed that concomitant 5-ASA use was not associated with increased odds of achieving clinical remission, mucosal healing, or biochemical remission in moderate to severe UC (12). Ungaro et al. (7) demonstrated that patients with CD who discontinued 5-ASA therapy with escalation to anti-TNF did not have increase in the need for new corticosteroid therapy, CD-related hospitalization, or surgery. There are currently no pediatric studies evaluating outcomes of patients who discontinue 5-ASA therapy, and our novel data suggests that discontinuation of 5-ASA after escalation to biologic therapy does not adversely affect clinical or biochemical outcomes.

Although 5-ASA medications are relatively inexpensive compared to other IBD therapies, they can incur a significant cost burden to patients and families (18,19). Our data demonstrate a cost savings of $6741 per patient, which could potentially reduce the financial burden for IBD treatment, especially for a medication that may not be providing any clinical benefit based on our data and prior studies. In addition to the cost of 5-ASA, they are also associated with adverse side effects, such as interstitial nephritis and pancreatitis, that may result in additional healthcare utilization and costs. IBD has significant quality of life (QOL) impacts on patients, including those related to medication burden. Patients have reported pill characteristics, timing, and number of pills prescribed, and need to carry medications around as key issues contributing to the burden and impact of IBD on their lifestyle (20). Although not formally evaluated in this retrospective study, patient QOL may be improved by decreasing the pill burden. With recent increased emphasis on high-value care, this study highlights the low clinical benefit compared to increased cost of care when using concomitant or continuing 5-ASA therapy in patients with IBD escalating to biologic therapy.

There are a few limitations of our study. This was a retrospective study, which may lend itself to selection and information bias. Our sample size was small, which limited the strength of our analyses and may lend them to be underpowered. In addition, it has been shown that clinical scores may not correlate well with the degree of intestinal inflammation (21,22). Inclusion of endoscopic data could provide further clarification on whether patients were escalated too quickly to biologic and distinguish those who were in remission based on sPCDAI but actually had mild intestinal inflammation and disease. Other limitations of our study were that we did not evaluate rate of surgeries and IBD-related hospitalizations, which are not only important clinical patient outcomes but also contribute significantly to the cost of care and patient QOL. Finally, a formal score for QOL was not assessed between the 2 groups. Despite these limitations, our results are consistent with prior studies.

In conclusion, we demonstrated that 5-ASA therapy is not an effective monotherapies for the treatment of pediatric patients with CD, as most of our patients required escalation of therapy. In addition, for those who require escalation to biologic therapy, there is no additional benefit to continuing 5-ASA treatment. Further prospective, randomized studies are needed to confirm these findings, as well as to better understand the role and impact of concomitant 5-ASA medications have on clinical outcomes, QOL, and healthcare utilization and costs for pediatric IBD patients who require escalation to biologic therapy.

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