Clinical Outcome Assessments in Pediatric Patients With Ulcerative Colitis and Crohn's Disease Receiving Biologics: A Retrospective Cohort Study

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Background: To assess disease activity, steroid-free remission, and other clinical outcome assessments among pediatric patients with ulcerative colitis (UC) and Crohn's disease (CD) in the ImproveCareNow (ICN) registry.

Methods: Patients aged 2–17 years diagnosed with UC or CD between June 1, 2013 and December 31, 2019 were enrolled if they initiated a biologic after enrollment in the ICN registry and completed at least 12 months follow-up after first maintenance dose. Baseline (at biologic initiation) demographics were summarized using descriptive statistics. Pediatric UC Activity Index (PUCAI), partial Mayo score, and Physician Global Assessment (PGA) were assessed for UC; and the Short Pediatric Crohn's Disease Activity Index (sPCDAI) and PGA were assessed for CD at first maintenance dose, 1- and 3-year time points. Kappa coefficients were used to assess the level of agreement between the outcome measures.

Results: A total of 1887 patients (UC = 350; CD = 1537) were included. Baseline demographics were similar across groups. For UC patients, mean PUCAI scores decreased and the proportion of patients in steroid-free remission, quiescent state based on PGA, and remission based on partial Mayo score increased from first maintenance dose to 1 and 3 years. For CD patients, mean sPCDAI score of CD patients decreased and the proportion of patients in steroid-free remission by sPCDAI and in quiescent state based on PGA increased from first maintenance dose to 1 and 3 years. Kappa coefficients showed only modest correlation between disease activity assessments.

Conclusions: Disease activity scores improved over time, with more pediatric patients with UC and CD achieving steroid-free remission at 1 and 3 years after first biologic maintenance dose.

Lay Summary

This real-world evidence demonstrated that biologic drugs improve disease activity scores in pediatric patients with ulcerative colitis and Crohn's disease over a period of 3 years from receiving their first maintenance dose. Majority of the patients achieved steroid-free remission during the course of the study.

Key Words: pediatrics, biologics, inflammatory bowel disease, ulcerative colitis, Crohn's disease

Introduction

Inflammatory bowel disease (IBD) including ulcerative colitis (UC) and Crohn's disease (CD), are chronic gastrointestinal disorders characterized by discontinuous phases of remission and relapse of active inflammation.[1,2] IBD affects around 6.8 million people globally.[3] In the United States, the pediatric prevalence of IBD is reported to have increased by 133%, from 33.0 per 100 000 population in 2007 to 77.0 per 100 000 population in 2016.[4]

Achieving and maintaining remission, optimizing growth and development, and avoiding complications are key approaches in the treatment of pediatric IBD.[5] However, pediatric IBD has an aggressive disease course and requires more frequent corticosteroid therapy than adult-onset IBD.[6,7] Long-term use of corticosteroids is not recommended due to adverse events and their general inability to sustain maintenance of remission.[8–10] Therefore, current clinical practices favor early initiation of biologics for better long-term outcomes.[11,12]

Current treatment approaches focus on steroid-free remission as an important outcome measure.[13,14]

Although biologics are known to have an impact on disease outcomes in IBD, patients and their caregivers often underestimate benefits and overestimate risks, delaying a decision to initiate biologics early.[13,15] Therefore, real-world data on clinical treatment patterns and comparative effectiveness are required to better understand the risks and benefits of IBD therapies, particularly in pediatric patients.[16] Clinical outcome assessments can be implemented, interpreted, and reported from the perspective of patient, clinician, or observer.[17] Data from the ImproveCareNow (ICN) network were used to assess disease activity, steroid-free remission, and other clinical outcome assessments among pediatric patients with UC and CD who initiated a biologic after their enrollment in the ICN registry.

Methods

Study Design and Patient Population

This retrospective and longitudinal analysis was conducted using the ICN database in patients who had visits between June 1, 2013 through December 31, 2019. ICN is a learning health network for pediatric IBD containing prospective and longitudinal data from outpatient encounters. Patients with IBD who are enrolled in the ICN network have their demographic data, disease activity, nutrition, growth, medication, and laboratory tests recorded at each visit.[18]

In the present study, patients aged 2–17 years with newly diagnosed UC or CD who initiated a biologic during the study period in ICN were included. Other inclusion criteria were: (1) provided written consent at sites in the United States, (2) data collected in ICN2 version of case report form, and (3) actively followed for at least 12 months after first maintenance dose. Patients with newly diagnosed UC or CD were defined as those with first ICN visit within 6 months of diagnosis. Baseline was defined as the time of biologic initiation. Diagnosis had to be consistent at enrollment and the most recent visit. Biologics included in the assessment were infliximab, adalimumab, certolizumab pegol, golimumab, natalizumab, ustekinumab, and vedolizumab.

Compliance With Ethics Guidelines

The study was conducted in full compliance with the US patient confidentiality requirements, including the Health Insurance Portability and Accountability Act of 1996. The study was approved by institutional review board vide protocol number 2019-1018.

Study Outcomes

Baseline demographics (age, sex, race, and ethnicity) and other clinical characteristics (height and weight) were assessed for all the patients who initiated a biologic and were actively followed for at least 12 months after initiation of biologics.

For patients with UC, all disease outcomes were assessed at 3 time points: (1) the time of the first maintenance dose of biologic (no induction is included), (2) 1 year after first maintenance dose, and (3) 3 years after first maintenance dose. The assessed disease outcomes included (1) mean Pediatric UC Activity Index (PUCAI) score; (2) disease severity status by PUCAI score of <10 as quiescent, 10–34 as mild, and ≥35 as moderate-to-severe; (3) the proportion of patients achieving steroid-free remission as defined by PUCAI score of <10 and no systemic steroid intake (prednisone or methylprednisolone) and rate of steroid use at each time point by diagnosis; (4) the proportion of patients by Physician Global Assessment (PGA: quiescent, mild, moderate, severe, or missing); and (5) the proportion of patients with partial Mayo clinical score (henceforth referred to as partial Mayo; range of 0–9), categorized as remission (<2), mild activity (2–4), moderate activity (5–7) and severe activity (>7). The partial Mayo was defined as the sum of stool frequency (range 0–3), rectal bleeding (range 0–3), and PGA (range 0–3) scores.

In patients with CD, the following outcome measures were reported at the first maintenance dose of biologic, and after 1 and 3 years: the Short Pediatric Crohn's Disease Activity Index (sPCDAI) scores (quiescent [<15], mild [15–29], moderate/severe [≥30]); the proportion of patients achieving steroid-free remission by as assessed by sPCDAI of <15 and no systemic steroid intake (prednisone or methylprednisolone) and rate of steroid use at each time point by diagnosis. PGA (quiescent, mild, moderate, severe, or missing) was also evaluated.

Some patients never reached PGA quiescent status at a study designated follow-up. Therefore, we also assessed whether a patient had any visits with PGA in quiescent state. The patients who initiated a biologic were analyzed at the specified time points irrespective of whether they continued on biologics.

Statistical Analysis

Descriptive statistics of baseline patient demographics was summarized by diagnosis and for the overall cohort. Categorical variables are presented as counts and percentages. Continuous variables are reported using means and SDs. The outcomes are summarized for the specified time points. The agreement between the PUCAI, partial Mayo, and PGA for patients with UC and sPCDAI, and PGA for patients with CD at different time points were estimated using kappa coefficients. The direction of the disagreement between sPCDAI and PGA and between PUCAI and PGA was calculated by adding the off-diagonal percentages from the corresponding contingency tables. It was separated by over- and underestimation based on the direction of the difference in severity. Bowker's tests of symmetry or McNemar's test were done for the null hypothesis of equal opportunity of over- and underestimation. No imputation was done for missing data, except for diagnosis date (if the diagnosis date was missing but diagnosis within the last 4 months was indicated, then the ICN enrollment date was used to impute the diagnosis date). Patients with missing values were excluded from the summaries of that variable.

Results

Patient Distribution and Demographics

Table 1 provides demographics and baseline characteristics of 1887 patients with UC (N = 350) or CD patients (N = 1537) who initiated a biologic during the study period and were followed actively for at least 12 months. Overall, the frequency of initiation of infliximab, adalimumab, certolizumab, ustekinumab, or vedolizumab was 1630 (79.9%), 323 (15.8%), 3 (0.15%), 20 (0.98%), and 64 (3.1%) patients, respectively, where the total N is greater than total number of patients because some patients had more than 1 biologic

Table 1. Demographic and baseline[a] characteristics.

	UC (*N* = 350)	CD (*N* = 1537)	Overall (*N* = 1887)
Age, mean years (SD)	13.1 (3.42)	12.9 (3.00)	12.9 (3.08)
Age group, *n* (%)			
2–5	11 (3.1)	21 (1.4)	32 (1.7)
6–11	69 (19.7)	385 (25.0)	454 (24.1)
12–18	270 (77.1)	1131 (73.6)	1401 (74.2)
Gender, *n* (%)			
Male	171 (48.9)	907 (59.0)	1078 (57.1)
Female	179 (51.1)	630 (41.0)	809 (42.9)
Race, *n* (%)			
Black	24 (9.5)	157 (13.4)	181 (12.7)
White	201 (79.8)	950 (80.8)	1151 (80.6)
Other	27 (10.7)	69 (5.9)	96 (6.7)
Missing	98	361	459
Ethnicity, *n* (%)			
Hispanic	33 (11.3)	63 (4.7)	96 (5.8)
Non-Hispanic	260 (88.7)	1287 (95.3)	1547 (94.2)
Missing	57	187	244
Weight (kg)			
N	346	1513	1859
Mean (SD)	55.3 (18.96)	49.7 (17.96)	50.7 (18.28)
Height (cm)			
N	342	1501	1843
Mean (SD)	158.0 (17.79)	154.7 (16.87)	155.3 (17.08)

Abbreviations: CD, Crohn's disease; SD, standard deviation; UC, ulcerative colitis.
[a]Baseline is at biologic initiation.

during the study period. At biologic initiation, patients with UC had mean (SD) age of 13.1 (3.4) years and 51.1% were female; patients with CD had a mean (SD) age of 12.9 (3.0) years, and 41.0% were female. The mean (SD) baseline weights of patients with UC and CD were 55.3 (19.0) and 49.7 (18.0) kg, respectively.

Clinical Outcome Assessments in Patients With UC

The mean (SD) PUCAI score of patients with UC decreased from 12.1 (16.16) at first maintenance dose to 5.7 (10.55) at 1 year and 3.7 (6.2) at 3 years; 56.7% of patients had quiescent disease activity at the first maintenance dose as assessed by PUCAI, increasing to 76.7% at 1 year and 80.4% at 3 years. Based on PGA, 67.2% of the patients had quiescent disease activity at first maintenance dose, increasing to 84.2% at 1 year and 92.6% at 3 years. Based on partial Mayo, 72.1% of patients were in clinical remission at the first maintenance dose, increasing to 87.5% at 1 year and 92.3% at 3 years (Table 2).

At first maintenance dose, the proportion of patients in steroid-free remission as assessed by PUCAI was 46.2%, which increased to 75.0% and 80.4% after 1 and 3 years, respectively (Figure 1). The proportion of patients using steroids at the first maintenance dose, at 1 year, and at 3-year time points was 90/384 (23.4%), 5/292 (1.7%), and 0/54 (0%), respectively. The kappa coefficients between PUCAI and PGA ranged from 0.46 to 0.55 in the period ranging from first maintenance dose to 3 years from first maintenance dose. The

kappa coefficient between PUCAI and partial Mayo ranged from 0.52 to 0.57, whereas for PGA and partial Mayo, it ranged from 0.70 to 1.00 at different time points (Table 3). PGA evaluated the disease as less severe than PUCAI in 11.8%–17.2% of the patients at different time points, while it evaluated the disease as more severe than PUCAI in 0%–8.1% in the cohort at each time point. These underestimations were observed significantly more often than the overestimations (*P* value from the symmetry test ranged from .03 to .0004, Table 4).

Clinical Outcome Assessments in Patients With CD

The mean (SD) sPCDAI score of patients with CD decreased from 9.5 (13.6) at first maintenance dose to 6.7 (11.0) at 1 year, and 6.3 (10.4) at 3 years. The disease activity status as assessed by sPCDAI was quiescent for 72.0% at the first maintenance dose; this increased to 82.5% and 86.1% at 1 year and at 3 years, respectively. The proportion of patients with CD who had quiescent disease activity based on PGA increased from 69.2% at first maintenance dose to 85.3% at 1 year and 89.6% at 3 years (Table 2).

The proportion of patients with CD in steroid-free remission as assessed by sPCDAI increased from 63.8% at first maintenance dose to 81.2% at 1 year and 85.4% at 3 years (Figure 1). The proportion of patients using steroids at the first maintenance dose, at 1 year, and at 3-year time points was 158/1656 (9.5%), 29/1384 (2.1%), and 2/368 (0.54%), respectively. For patients with CD, the kappa coefficient

Table 2. Disease outcomes at specified time points.

	First maintenance dose (N = 384)[a]	1 year from first maintenance dose (N = 292)[a]	3 years from first maintenance dose (N = 54)[a]
PUCAI			
N	367	283	51
Mean (SD)	12.1 (16.16)	5.7 (10.55)	3.7 (6.23)
Min–Max	0.0–85.0	0.0–65.0	0.0–25.0
Steroid-free remission by PUCAI			
Yes	171 (46.2%)	213 (75.0%)	41 (80.4%)
Disease severity status by PUCAI			
Quiescent	208 (56.7%)	217 (76.7%)	41 (80.4%)
Mild	114 (31.1%)	56 (19.8%)	10 (19.6%)
Moderate/severe	45 (12.3%)	10 (3.5%)	0 (0.0%)
Physician Global Assessment			
Quiescent	252 (67.2%)	246 (84.2%)	50 (92.6%)
Mild	83 (22.1%)	37 (12.7%)	4 (7.4%)
Moderate/severe	40 (10.4%)	9 (3.1%)	0 (0.0%)
Partial Mayo score[b]			
0	215 (58.3%)	215 (74.9%)	42 (80.8%)
1	51 (13.8%)	36 (12.5%)	6 (11.5%)
2	36 (9.8%)	16 (5.6%)	4 (7.7%)
3	20 (5.4%)	8 (2.8%)	0 (0.0%)
4	22 (6.0%)	8 (2.8%)	0 (0.0%)
5	12 (3.3%)	2 (0.7%)	0 (0.0%)
6	4 (1.1%)	1 (0.3%)	0 (0.0%)
7	5 (1.4%)	1 (0.3%)	0 (0.0%)
8	2 (0.5%)	0 (0.0%)	0 (0.0%)
9	2 (0.5%)	0 (0.0%)	0 (0.0%)
Partial Mayo score[b] group			
Remission	266 (72.1%)	251 (87.5%)	48 (92.3%)
Mild	78 (21.1%)	32 (11.1%)	4 (7.7%)
Moderate/severe	25 (6.8%)	4 (1.4%)	0 (0.0%)

	First maintenance dose (N = 1656)[a]	1 year from first maintenance dose (N = 1384)[a]	3 years from first maintenance dose (N =368)[a]
sPCDAI			
N	1069	1163	280
Mean (SD)	9.5 (13.63)	6.7 (11.01)	6.3 (10.40)
Min–Max	0.0–75.0	0.0–80.0	6.3 (10.40)
Steroid-free remission by sPCDAI[c]			
Yes	729 (63.8%)	949 (81.2%)	239 (85.4%)
No	413 (36.2%)	220 (18.8%)	41 (14.6%)
Disease severity status by sPCDAI			
Quiescent	770 (72.0%)	960 (82.5%)	241 (86.1%)
Mild	175 (16.4%)	132 (11.3%)	25 (8.9%)
Moderate/severe	124 (11.6%)	71 (6.1%)	14 (5.0%)
Physician Global Assessment			
Quiescent	1120 (69.2%)	1171 (85.3%)	327 (89.6%)
Mild	389 (24.0%)	163 (11.9%)	28 (7.7%)
Moderate/severe	109 (6.6%)	39 (2.8%)	10 (2.7%)

Abbreviations: PUCAI, Pediatric Ulcerative Colitis Activity Index; SD, standard deviation; sPCDAI, Short Pediatric Crohn's Disease Activity Index.
[a]N is the number of patients on biologics specified in the study who had a visit at the specified time points.
[b]Partial Mayo score = stool frequency score + rectal bleeding score + Physician Global Assessment score.
[c]Denominator for calculating the percentages is number of patients with steroid-free remission and no steroid-free remission.
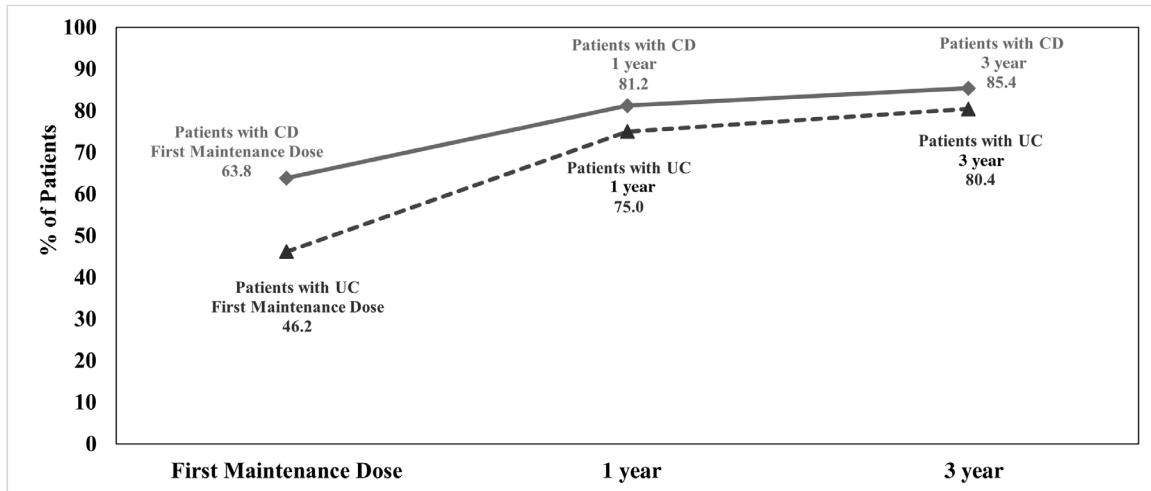
Figure 1. Steroid-free remission among pediatric patients with UC and CD receiving biologic therapy. Abbreviations: CD, Crohn's disease; UC, ulcerative colitis.

Table 3. Kappa coefficients between disease outcomes at specified time points.

Patient population	Outcomes	First maintenance dose K (CI)	1 year from first maintenance dose K (CI)	3 years from first maintenance dose K (CI)
Crohn's disease	sPCDAI and PGA	0.43 (0.38, 0.48)	0.41 (0.35, 0.47)	0.40 (0.26, 0.55)
Ulcerative colitis	PGA and partial Mayo score	0.73 (0.66, 0.79)	0.70 (0.59, 0.81)	1.00 (1.00, 1.00)
	PUCAI and PGA	0.55 (0.47, 0.63)	0.46 (0.35, 0.57)	0.52 (0.20, 0.84)
	PUCAI and partial Mayo score	0.57 (0.49, 0.65)	0.54 (0.43, 0.66)	0.52 (0.20, 0.84)

Abbreviation: CI, confidence interval; K, kappa coefficient; PGA, Physician Global Assessment; PUCAI, Pediatric Ulcerative Colitis Activity Index; sPCDAI, Short Pediatric Crohn's Disease Activity Index.

Table 4. Percent agreement between PUCAI/sPCDAI with PGA.

Outcome 1	Outcome 2	Time point	Agree	PGA overestimation	PGA underestimation	Symmetry test P
sPCDAI	PGA	Start	75.05	10.08	14.88	<.0001
		1 year	83.92	5.07	11.01	<.0001
		3 years	88.22	1.43	10.35	.0002
		Discontinue	68.87	12.68	18.44	.0007
PUCAI	PGA	Start	75.9	6.93	17.17	.0004
		1 year	82.33	4.59	13.07	.0018
		3 years	88.23	0	11.76	.0143
		Discontinue	79.03	8.07	12.9	.0343

Abbreviations: PGA, Physician Global Assessment; PUCAI, Pediatric Ulcerative Colitis Activity Index; sPCDAI, Short Pediatric Crohn's Disease Activity Index. The entries for agreement, PGA overestimation, PGA underestimation are % of the subjects fall in each categories at each time point. The sum of these 3 numbers should add up to 100% (difference are due to rounding error). The symmetry tests are McNemar's test for 2 × 2 table and Bowker's test for larger $n \times n$ table. The null hypothesis of these tests is the chances of over- or underestimate are equal.

between sPCDAI and PGA ranged from 0.40 to 0.43 from first maintenance dose to 3 years from first maintenance dose (Table 3). PGA evaluated the disease as less severe than sPCDAI in 10.4%–18.4% of the patients at different time points, while it evaluated the disease as more severe than sPCDAI in 1.4%–12.7% in the cohort at each time point. These underestimations were significantly observed more often than the overestimations (P value from the symmetry test ranged from 0.0007 to <0.0001, Table 4).

Subset Analysis of Patients With UC and CD With PGA = Quiescent

This subset analysis was based on whether patients with UC and CD had any visits with PGA status = quiescent. Demographics and disease outcomes for these patients are reported in Supplementary Tables S1 and S2. Disease outcome results for patients with UC and CD who had one or more visits with PGA as quiescent were similar to the original cohort. Seven patients with UC had no visits with PGA

= quiescent and their mean (SD) PUCAI score changed from 43.8 (25.9) at first maintenance dose to 33.8 (20.2) after 1 year. Nineteen patients with CD had no visits with PGA = quiescent and their mean (SD) sPCDAI score was 22.9 (16.0) at first maintenance dose and changed to 23.5 (17.5) after 1 year (Supplementary Table S3).

Discussion

This was a large retrospective study representing nationwide data from the United States that assessed disease outcome measures in 1887 pediatric patients with UC or CD, who received a biologic as maintenance therapy. Our findings suggest that disease activity scores improve over time and that more than 75% and 80% of pediatric patients with UC or CD achieve steroid-free remission by 1 and 3 years from the first biologic maintenance dose, respectively. There was a modest correlation between disease activity assessments. PGA and partial Mayo had the strongest level of agreement between them as assessed by kappa coefficient.

Several observational studies have established the use of clinical indices for assessing disease activity in pediatric patients with IBD.[19,20] However, the correlation between measures such the PUCAI, PGA, and partial Mayo score still needs to be fully established in the pediatric IBD population. In our study, we found good to very good correlation between PGA and partial Mayo with the kappa coefficients ranging between 0.73 and 1.0 from first maintenance dose to 3 years from maintenance dose in patients with UC. However, it is notable that the partial Mayo scores is inclusive of PGA, so a higher correlation might be anticipated. The other kappa coefficients values showed only fair to moderate correlations between disease activity measures, based on the guidance from Landis and Koch.[21] A previous study by Kappelman et al observed the Spearman correlation coefficient between sPCDAI and PGA to be 0.6,[22] which is more than the 0.4–0.43 observed in our study. This could be due to missing confounders.

The current treatment strategy in pediatric IBD is targeted towards clinical remission, sustaining steroid-free remission, and ensuring mucosal/transmural healing while maintaining growth, supporting nutrition, improving quality of life, and minimizing adverse events.[23–25] In addition, the use of corticosteroids can result in side effects such as bone loss and risk of osteoporosis, glaucoma, increased risk of diabetes and cardiovascular diseases, thromboembolism, poor wound healing, and increased risk of mortality.[26] A previous study by ICN also observed decreased use of corticosteroids among pediatric patients over time.[27] Another study recommends use of steroid-sparing therapy for treatment of patients with CD to reduce the risk of perianal fistulizing complications.[28] Hence, avoidance of corticosteroids is an important patient- and physician-preferred treatment goal for managing UC and CD in clinical practice.[26]

Despite the scarcity of data on clinical efficacy and safety of biologics in pediatrics, there have been favorable clinical outcomes in adult IBD populations and biologics have been included in the treatment algorithm for pediatrics.[29,30] An earlier registry on pediatric patients with IBD from the Sicilian Network assessing the efficacy and safety of biologics found that biologics are effective in inducing remission and achieving sustained clinical benefits.[31] Their study also observed that a longer duration of disease and later start of therapy could result in reduced short- and long-term effectiveness.[31] Our findings are consistent with the Sicilian Network study. We report improved PUCAI scores, sPCDAI scores, and steroid-free remission over a 3-year period in pediatric patients who receive biologics as maintenance therapy.

Clinical studies on biologics, such as infliximab, adalimumab, vedolizumab, and ustekinumab have already shown efficacy in treating adult patients with UC and/or CD.[20,32–36] However, more evidence from real-world data is required in the pediatric population as this population is often awaiting completion of clinical trials in adult patients. Our study provides an overview of clinical outcome assessments along with PGA measures in both UC and CD.

Strengths and Limitations

A strength of our study is the large and geographically varied dataset from the ICN network that allowed us to retrospectively analyze the real-world evidence of disease outcomes for over 3 years in pediatric IBD population with a large sample size. Despite a larger population of pediatric patients in the registry, 1 limitation is the small proportion of patients with 3 years follow-up data. Another limitation is that the use of biologics may have evolved over the duration of this study, therefore, many patients might have initiated different treatment earlier, but were receiving newer biologics at the end of the follow-up period. Our study lacks colonoscopy findings to substantiate the results further.

Conclusion

This study found that disease activity improves over time among pediatric patients with UC and CD who initiate maintenance biologics. Steroid-free clinical remission increased significantly at 1 and 3 years after initiating maintenance biologics. PGA and partial Mayo clinical score had the strongest level of agreement and there were modest levels of agreement observed between other disease activity assessments as well.

Supplementary Data

Supplementary data is available at *Crohn's and Colitis 360* online.

Acknowledgment

Authors' Contributions

All the authors participated in conception and design of the study. Data acquisition was by Richard B. Colletti, Chunyan Liu, and Nanhua Zhang. Chunyan Liu and Nanhua Zhang did the analysis of data. Interpretation of the data was done by all authors. All authors participated in critical revision of the manuscript for important intellectual content.

Funding

Conflicts of Interest

Data Availability

The datasets analyzed during the current study are from the ImproveCareNow Registry and are not available publicly. Data can be made available from the corresponding author upon a reasonable request.

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