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Observations and Research

Extraintestinal Manifestations of Inflammatory Bowel Disease Are Associated With Increased Biologic Cycling

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Background: Extraintestinal manifestations (EIMs) of inflammatory bowel disease (IBD) are a common, frequently debilitating complication of the disease. Biologics are indicated and often required in patients with EIMs to control disease; however, little is known about whether patients with EIMs cycle through more therapies than their counterparts without EIMs.

Methods: To address this question, we performed a retrospective analysis of patients enrolled in the Study of Prospective Adult Research Cohort with IBD registry seen at our University Medical Center, on data from December 2016 to January 2021. Four hundred fifty-six participants with information on EIMs and biologic use available were included, and demographic and clinical characteristics were analyzed.

Results: Three hundred thirty-eight and 118 participants without and with EIMs were identified, respectively. Those with EIMs were likelier to have biologic exposure, and cycle through more biologics, both in univariate and multivariate analyses controlling for age, disease duration, sex, corticosteroid use, and IBD type (*P*-value = .006). In a subanalysis of patients with Crohn's disease (CD), EIMs were associated with increased biologic cycling in ileocolonic disease (P-value = .050).

Conclusions: To our knowledge, this is the first study assessing biologic cycling in patients with EIMs. Our findings that patients with EIMs are likelier to cycle through biologics, particularly CD patients with ileocolonic disease, highlights the need for more research on which biologics may be most effective for specific subsets of IBD patients, including those with concurrent EIMs. The presence of EIMs is a marker of harder-to-treat IBD and may indicate earlier initiation of advanced therapies.

Lay Summary

Though extraintestinal manifestations (EIMs) frequently occur in inflammatory bowel disease, data regarding their association with biologic therapy cycling are sparse. We found patients with EIMs cycle through more therapies, and in Crohn's disease, this is associated with ileocolonic involvement.

Key Words: inflammatory bowel disease, extraintestinal manifestations, biologic therapy, SPARC

Introduction

Inflammatory bowel disease (IBD) is an umbrella term for a group of chronic diseases, the most common of which are Crohn's disease (CD) and ulcerative colitis (UC), causing autoimmune intestinal and extraintestinal inflammation. Systemic, multiorgan involvement in the form of extraintestinal manifestations (EIMs) is a common complication, while musculoskeletal involvement most frequently occurs, and dermatologic, ocular, and/or hepatobiliary involvement is regularly observed. EIMs develop more often in CD,[1] particularly arthritis, uveitis, and erythema nodosum (EN).[2,3] Certain phenotypes such as colonic disease in CD[4] and more extensive colonic involvement in UC[1] are also associated with increased risk. While some EIMs, such as EN, episcleritis, and peripheral inflammatory arthritis, are more likely associated with active intestinal disease, others such as uveitis, primary sclerosing cholangitis (PSC), and ankylosing spondylitis are not.[5,6] Further, some EIMs such as pyoderma gangrenosum (PG), and in some individuals, peripheral arthritis, have an unclear relationship with disease activity.[5,6] Regardless, onset or recurrence of EIMs can be associated with a lack of mucosal healing,[7] may be a marker of more aggressive disease,[8] is predictive of younger age of IBD diagnosis in adults[9] and increased risk of pouchitis,[10] and is more common in pediatric-onset UC.[11]

Biologic use in IBD is frequently employed in those with predictors of an aggressive disease course and in those with moderate-to-severe disease.[12] Use of any effective therapy including biologics to control intestinal disease activity can aid in controlling EIMs driven by intestinal inflammation. Additionally, anti-tumor necrosis factor (anti-TNF) biologics and Janus kinase inhibitors can be effective for EIMs that have an independent disease course whereas novel biologics like ustekinumab, risankizumab, and vedolizumab may be less effective. Optimal therapeutic control of EIMs is important given that patients with EIMs are more likely to have disability and decreased quality of life, independent of intestinal disease activity and phenotype.[13] However, while patients with EIMs are known to require more aggressive therapies, little is known about how often patients with EIMs must switch therapies compared to those without EIMs. We began bridging this gap by assessing the rate of

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biologic cycling in individuals with IBD with versus without EIMs.

Materials and Methods

Study Design and Population

Initiated in 2016, the Study of a Prospective Adult Research Cohort with IBD (SPARC) is deeply characterizing and phenotyping thousands of IBD patients across 17 sites throughout the United States, with the goal of improving precision medicine in IBD. Data on patient-reported outcomes, endoscopic, laboratory, and pathologic findings, as well as omics data are collected and generated. We performed a retrospective review and analysis of data collected between December 2016 and January 2021 at our University site. The study was approved by our University Human Research Protections Office on 09/23/2020.

Inclusion/Exclusion Criteria

Participants, who were at least 18 years of age, had received a confirmed diagnosis of either CD or UC by clinical, endoscopic, histologic, or radiologic criteria as listed on the IBD Smart Form were included. Participants were required to have complete information on the history of EIMs (arthritis, uveitis/iritis, PG, EN, and PSC) included in the Smart Form, and to be included in this analysis, needed to verifiably have no history of biologic exposures, or at least 1 exposure. IBD-associated arthritis was a comprehensive category that included peripheral arthropathy, isolated sacroiliitis, and ankylosing spondylitis. At baseline, not all Smart Forms had a complete drug exposure history. For example, if a patient had complete information available on positive anti-TNF exposure at baseline, but had incomplete information on vedolizumab and ustekinemab, they were still eligible to participate. However, if they had no known anti-TNF exposure at baseline and had incomplete information on vedolizumab and ustekinemab available, they were not eligible.

Outcome

Our primary outcome of interest was the number of biologics used in those with versus without EIMs; the primary outcome data were initially collected and recorded by clinicians during the participant SPARC intake visit. Biologic therapies included adalimumab, infliximab, certolizumab, golimumab, ustekinumab, and vedolizumab. Dichotomized exposure status for each biologic listed on the IBD smart form (ever or never) was used, and was updated at follow-up visits, such that all biologic use up until January 2021 could be captured in the dataset. It is possible that participants received other biologic therapies for the treatment of EIMs. However, this number would be very small.

Data Collection and Study Variables

Demographic and clinical variables were extracted from baseline information entered by providers and research staff into the IBD Smart Form. Although patients are followed longitudinally, only the initial enrollment visit was used for the purposes of this study. Variables extracted included sex, race, birth year, age at inclusion, age at diagnosis, IBD type (CD, UC), CD behavioral phenotype (inflammatory, stricturing, penetrating), CD disease location (Ileal, ileocolonic, and colonic), CD perianal disease behavior (yes or no), CD upper tract involvement (yes or no), UC extent of disease (proctitis, left-sided, extensive/pancolitis), tobacco use within the last 3 months (yes or no), corticosteroid exposure (ever or never), and information on EIMs (described above). Disease duration was calculated based on birth year and age of diagnosis.

Statistical Analysis

Baseline demographic and clinical characteristics of our study population were performed based on EIM presence and biological exposure. We calculated the mean and interquartile range (IQR) for continuous data and proportions for categorical data. Welch's *t*-test was used to assess differences in means and differences in proportions were assessed using a Fisher's exact test, with a Fisher's multiple comparison utilized for differences in proportions between specific subgroups. Biologic use in various subgroups was compared using univariate linear regression (via Generalized Linear Modeling, Gaussian family). Using mixed multiple linear regression, we estimated the association between EIMs and biologic use, while controlling for potential confounders. Only participants with complete information on all biologics in the Smart Form were included in linear regression analyses. All statistical analyses were carried out using R version 4.0.4 with the "stats,"[14] "vctrs."[15] "oddsratio,"[16] and "RVAideMemoire"[17] packages.

Ethical Considerations

Study participants were identified from the institutional review board-approved clinical data repository and this study was approved by our University's Human Research Protections Office. A waiver for consent was granted for our retrospective analysis.

Results

Demographic and Clinical Characteristics of Participants

A total of 555 participants had data available, with 11 participants having missing data on their history of EIMs, and 88 missing data on biologic exposure, resulting in a final cohort of 456 participants. Participant demographics and disease-related characteristics were assessed based on EIM status, defined as having 0 or ≥1 EIM, and are summarized in Table 1. IBD-associated arthritis was reported in 78 participants, EN in 18, uveitis/iritis in 14, PSC in 10, and PG in 5 participants. Participants with 1 or more EIM were older at inclusion than those with 0 EIMs (45.0 vs. 41.3 years of age; *P*-value = .012) and had been diagnosed with IBD for longer (19.2 vs. 14.6 years; *P*-value < **.001**), with no difference in age of diagnosis. No differences in sex, race, corticosteroid exposure, recent tobacco use (in the 3 months prior), or diagnosis (UC vs. CD) were observed in those with versus without EIMs.

The Relationship Between EIMs and Disease Phenotype

Participants with 1 or more EIMs were less likely to have upper tract disease (17.6% vs. 24.0% in those without

Table 1. Baseline demographic and clinical characteristics of participants with IBD by number of extraintestinal manifestations from our university IBD program enrolled in SPARC IBD. Bolded p-values are ≤ 0.05.

Variable	Overall, n = 456	No EIMs, n = 338 (74.1%)	At least 1 EIM, n = 118 (25.9%)	p-value
Age at inclusion in years, mean (IQR)	42.2 (31, 51) Range: (19, 86)	41.3 (31, 49.8) Range: (19,86)	45.0 (34, 56) Range: (22,80)	**.012**
Age at diagnosis in years, mean (IQR)	26.4 (17, 32) Range: (5, 70)	26.6 (17, 32) Range: (5, 70)	25.7 (17, 31) Range: (7, 68)	.507
Diagnosis				.100
UC	132 (28.9%)	105 (31.1%)	27 (22.9%)	
CD	324 (71.1%)	233 (68.9%)	91 (77.1%)	
Sex				.336
Female	203 (44.5%)	155 (45.9%)	48 (40.7%)	
Race				.638
White	373 (81.8%)	273 (80.8%)	100 (84.7%)	
Black	57 (12.5%)	44 (13.0%)	13 (11.0%)	
Other		21 (6.2%)	5 (4.2%)	
Disease duration in years, mean (IQR)	15.8 (8, 21) Range: (1, 56)	14.6 (7, 19) Range: (1, 56)	19.2 (12, 25) Range: (2, 47)	**<.001**
Biologic exposure (to at least 1 biologic)	384 (84.2%)	285 (84.3%)	109 (92.4%)	**.029**
Number of biologics				**.007**
0	62 (13.6%)	53 (15.7%)	9 (7.63%)	
1	115 (25.2%)	89 (26.3%)	26 (22.0%)	
2+	173 (37.9%)	115 (34.0%)	58 (49.2%)	
Unknown if 1 or 2 + biologics	106 (23.3%)	81 (24.0%)	25 (21.2%)	
Number of biologics	1.20 (1, 2) Range: (0, 5)	1.09 (0, 2) Range: (0, 4)	1.46 (1, 2) Range: (0, 5)	**.005**
Precise number of biologics unknown	203 (44.5%)	146 (43.2%)	57 (48.2%)	.390
Tobacco use in past 3 months	40 (8.8%)	32 (9.47%)	8 (6.78%)	.696
Corticosteroid exposure	375 (82.2%)	278 (82.2%)	97 (82.2%)	.488
CD disease behavior				.736
Inflammatory	124 (38.4%)	92 (39.5%)	32 (35.1%)	
Stricturing	87 (26.9%)	63 (27.0%)	24 (26.4%)	
Penetrating	101 (31.1%)	70 (30.0%)	31 (34.1%)	
Unknown	12 (3.7%)	8 (3.4%)	4 (4.4%)	
Perianal disease[a]	208 (64.2%)	148 (63.5%)	60 (65.9%)	.327
CD disease location				**.020**
Ileal	109 (33.6%)	86 (36.9%)	23 (25.3%)	
Colonic	55 (17.0%)	43 (18.5%)	12 (13.2%)	
Ileocolonic	147 (45.4%)	94 (40.3%)	53 (58.2%)	
Unknown	12 (3.7%)	9 (3.86%)	3 (3.30%)	
Upper tract disease[b]				**.029**
Present	72 (22.2%)	56 (24.0%)	16 (17.6%)	
Absent	240 (74.1%)	168 (72.1%)	72 (79.1%)	
Unknown	12 (3.7%)	9 (3.86%)	3 (3.30%)	
UC disease location				.367
Proctitis	3 (3.0%)	3 (2.86%)	1 (3.70%)	
Left-sided disease	36 (27.2%)	32 (30.5%)	4 (14.8%)	
Extensive/pancolitis	70 (53.3%)	57 (54.3%)	13 (48.1%)	
Unknown	22 (16.7%)	13 (12.4%)	9 (33.3%)	

Abbreviations: CD, Crohn's disease; EIM, extraintestinal manifestation; IBD, inflammatory bowel disease; IQR, interquartile range; SPARC, Study of a Prospective Adult Research Cohort with IBD; UC, ulcerative colitis.
[a]Perianal disease may coexist with other behavioral phenotypes.
[b]Disease modifier may coexist with other disease locations.

EIMS, *P*-value = .029), and more likely to have ileocolonic compared to ileal disease location (58.2% vs. 25.3% respectively), compared to participants without EIMs (40.3% and 36.9%, respectively; Fisher's multiple comparison with FDR correction *P*-value = .027). No differences in UC disease location, CD disease behavior, or rate of perianal disease were observed between those with versus without EIMs.

Association of EIMs With Biologic Sequencing

The likelihood of exposure to at least 1 biologic differed between those with versus without EIMs, with 92.4% of participants with at least 1 EIM having biologic exposure versus 84.3% of those without (*P*-value = .0289); participants with EIMs also had a higher likelihood of being exposed to more than 1 biologic than those without (49.2% vs. 34.0%, Fisher's multiple comparison with FDR correction *P*-value = .0150). Participants with 1 + EIM had a higher mean number of biologic exposures than those without an EIM (1.46 vs. 1.09 biologics used per participant, *P*-value = .00482; Figure 1).

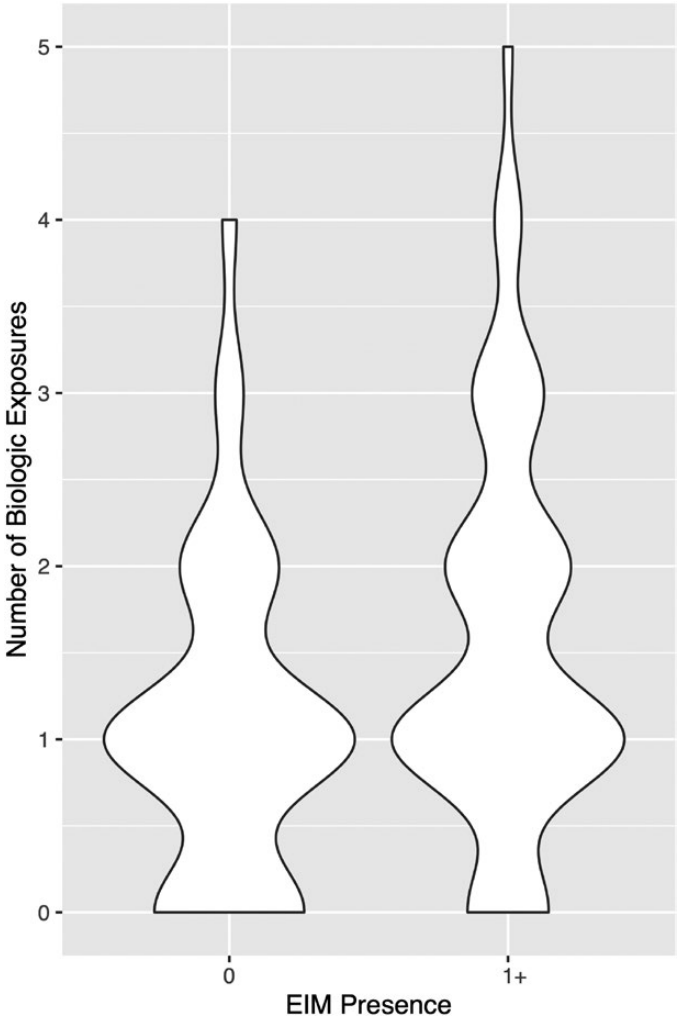

Figure 1. Violin plot of biologic exposures in participants with versus without extraintestinal manifestations with inflammatory bowel disease from the SPARC Cohort at our University.

Table 2. Crude association of demographic and clinical characteristics of SPARC participants by number of biologics from our University Inflammatory Bowel Disease Program enrolled in SPARC IBD. Bolded p-values are ≤ 0.05.

Variable	Value of relationship with number of biologics (*n* = 253)	*P*-value
Age at inclusion in years	−0.00471	.309
Age at diagnosis in years	**−0.0101**	**.037**
Diagnosis		
UC relative to CD	**−0.533**	**<.001**
Sex		
Female relative to male	−0.228	.075
Race		
Black relative to White	0.0475	.809
Other relative to White	−0.287	.325
Disease duration in years	0.0105	.119
Tobacco use in past 3 months	−0.00106	.996
Corticosteroid exposure	**0.651**	**<.001**
CD disease behavior		
Penetrating (relative to inflammatory)	0.196	.286
Stricturing (relative to inflammatory)	**0.484**	**.015**
Perianal disease[a]	**0.583**	**<.001**
EIMs		
1 + EIM relative to 0 EIM	**0.469**	**.002**
CD disease location (*n* = 203)		
Colonic relative to ileal disease	0.0388	.856
Ileocolonic relative to ileal disease	**0.420**	**.017**
Presence of upper tract disease[b]	−0.254	.128
UC disease location (*n* = 61)		
Left-sided disease relative proctitis	0.722	.162
Pancolitis relative to proctitis	0.850	.088

Abbreviations: CD, Crohn's disease; EIM, extraintestinal manifestation; SPARC, Study of a Prospective Adult Research Cohort with IBD; UC, ulcerative colitis.
Generalized linear models were used to assess the relationship between number of biologics and several demographic data and clinical characteristics of disease.
[a]This is a disease modifier and may coexist with other behavioral phenotypes.
[b]This is a disease modified and may coexist with other disease locations.

Biologic Use and Demographic and Clinical Confounders

To account for the high likelihood of confounding, the relationship between biologic sequencing and the above demographic and clinical characteristics was assessed using a series of Generalized Linear Models (Table 2 The number of biologics a participant had sequenced through had no relationship with their age, sex, race, disease duration, recent tobacco use, presence of upper tract disease, or UC disease location. A slight increase in the number of biologics used was observed in participants who were younger at diagnosis, with a nearly 1% decrease in biologics used for each additional year of age at diagnosis relative to the cohort

mean (*P*-value = .037). Additionally, an increase in biologic sequencing was observed in participants with corticosteroid exposure, with an increase in the mean of 0.651 biologics (or 54.3% increase relative to the cohort mean) used in those who had also used corticosteroids (*P*-value < .001). Participants with higher biologic sequencing were also more likely to have CD (decrease in the mean of 0.533 or 44.4% in UC participants, *P*-value < .001), and in those with CD, were more likely to have stricturing disease (40.3% increase in number of biologics relative to inflammatory disease, *P*-value = .015) and perianal disease (48.6% increase, *P*-value < .001). Additionally, CD participants with ileocolonic disease (vs. ileal disease) had a 35% increase in biologic use relative to the cohort mean (*P*-value = .017).

Association of EIMs and Biologic Sequencing

Using a mixed linear multiple regression model, EIM group was assessed as a predictor of the number of biologics a participant used (Table 3). This was done while controlling for corticosteroid use, disease duration, diagnosis, and for sex and age. Participants with 1 or more EIM were more likely to use more biologics, with the mean number of biologics used by EIMs being 0.399 greater than their counterpart group with no EIMs or a 33.3% increase relative to the cohort mean (*P*-value = .006). Once all other factors were controlled for, disease duration and age were not found to be predictors of increased biologic sequencing, nor was sex. Participants with corticosteroid exposure and CD were also likelier to sequence through more biologics, with the mean number of biologics in each subgroup being 0.692 and 0.530 higher than their nonsteroid and UC counterparts (or 57.7% and 44.2% higher than the cohort mean, *P*-values < .001).

The Relationship Between EIMs, Disease Location, and Biologic Use

Given the association of biologic sequencing with stricturing, perianal, and ileocolonic disease in CD, and the overlapping association of EIMs with ileocolonic disease, a separate model looking only at biologic sequencing in CD participants was developed (Table 4). Due to the status of perianal disease and disease location being unknown for a subset of participants, this resulted in 114 participants being included in the model. EIM presence was again used as a predictor of number of biologics used, while also controlling for corticosteroid use, presence/absence of perianal disease, disease behavior, disease location, the interaction between EIM presence and disease location, and sex. Participants with penetrating and stricturing disease were likelier to sequence through biologics than those with inflammatory disease, with mean biologic use in each group being 0.630 and 0.755 or 44.5% and 53.3% above the mean of all participants included in the model, respectively (*P*-values = .009 and .003, respectively). When the interactions between EIM presence and disease location were accounted for in the model, neither EIMs nor disease location alone were predictive of increased biologic sequence. However, the interaction between EIM presence and disease location was significant; participants with ileocolonic disease who had EIMs were likelier than those with EIMs and ileal disease to sequence through more biologics, with a mean increase of 0.894 more biologics used (63.2%; *P*-value = .050). When controlling for all other factors, perianal disease was found not to have a statistically significant relationship with biologic sequencing.

Table 3. Mixed linear multiple regression comparing various participant factors as predictors of number of biologics used. Bolded p-values are ≤ 0.05.

Factor	Regression value (β)	p-value[a]
Diagnosis (UC relative to CD)	**−.530**	**<.001**
Age at inclusion	−.005	.317
1 EIM (relative to 0 EIMs)	**.399**	**.006**
Disease duration	.010	.196
Female relative to male sex	−.217	.089
Corticosteroid use	**.692**	**<.001**

Abbreviations: CD, Crohn's disease; EIM, extraintestinal manifestation; UC, ulcerative colitis.
[a]From mixed linear regression model.

Table 4. Mixed linear multiple regression comparing various participant factors as predictors of number of biologics used in Crohn's disease participants from our University IBD program enrolled in SPARC IBD. Bolded p-values are ≤ 0.05.

Factor	Regression value (β)	p-value[a]
Female (relative to male sex)	−.240	.206
1 EIM (relative to 0 EIMs)	−.160	.643
Corticosteroid use	**.872**	**.002**
Penetrating (relative to inflammatory disease)	**.630**	**.009**
Stricturing (relative to inflammatory disease)	**.755**	**.003**
Presence of perianal disease	−.710	.477
Colonic (relative to ileal disease)	.549	.096
Ileocolonic (relative to ileal disease)	.389	.139
Interaction between EIM presence and colonic disease (relative to ileal disease)	−.011	.985
Interaction between EIM presence and ileocolonic disease (relative to ileal disease)	**.894**	**.050**

Abbreviations: EIM, extraintestinal manifestation; IBD, inflammatory bowel disease; SPARC, Study of a Prospective Adult Research Cohort with IBD.
[a]From mixed linear regression model.

Discussion

In our study, participants with EIMs were likelier to cycle through more biologic therapies, even when accounting for potentially confounding factors that were also associated with biologic cycling such as corticosteroid use, disease duration, diagnosis, age, and sex. Participants with EIMs were slightly older, with slightly longer disease duration than those without EIMs. Further, ileocolonic disease was associated both with EIMs and with increased mean biologic exposures, confirming that ileocolonic disease is a marker of aggressive disease. This corresponds with prior findings that ileocolonic disease is associated with higher rates of surgery in CD patients.[18] In our multivariate model assessing EIMs and biologic exposure exclusively in the CD population, we found

that those with EIMs and ileocolonic disease were likelier to cycle through more biologic therapies. While we did not have data available on why biologic switching occurred, the goal of our study was to assess frequency in those with vs without EIMs, which we were able to successfully do. Altogether, our results suggest that the presence of EIMs, especially in patients with CD with ileocolonic disease location, is associated with the increased use of biologic therapy, potentially indicating that patients with EIMs have more difficulty controlling the disease.

Given prior research on the association between EIMs and ileocolonic disease,[19,20] it is not surprising that we found a positive relationship between the two in our cohort. Ileocolonic disease is also associated with higher rates of surgery,[18] particularly in the first 3 years following diagnosis,[21] and is also associated with increased recurrence following surgery.[22,23] Further, ileocolonic disease is associated with a higher rate of conversion to stricturing or penetrating,[23–25] and disabling disease.[25] The associations between ileocolonic disease and increased rates of disease complications highlight the importance of recognizing the interrelationships between these complications, including looking at EIMs as a potential predictor of a refractory disease, impaired quality of life, and complexity of care. Further work is required to explore this relationship.

The lack of a significant correlation between sex and diagnosis with EIMs at the univariate level in our cohort was surprising. Female sex has been associated with the development of EIMs in a number of cohorts, with significant geographic diversity.[26–29] CD (relative to UC) also has an increased association with EIMs, except for PSC.[28–30] Thus, the lack of association between EIMs and these factors in our cohort is suggestive that other unmeasured confounding variables regarding EIM development were present, prior associations noted are less relevant in modern cohorts, and/or larger sample sizes are needed to identify these associations.

Limitations of our study include the retrospective nature and our study size. While incredibly helpful for hypothesis formation and initial findings, dissecting confounding variables in retrospective studies can be difficult. Further, the chance of misclassification is increased, including in EIM presence, making it imperative that findings from retrospective studies are validated in prospective cohorts. Additionally, while our cohort of 456 participants is of a reasonable size, the subcohort of patients with EIMs was comprised of 118 individuals, making it more difficult to assess minor differences that may exist in subpopulations with EIMs. Further, the subgroup of participants included in the CD-specific analysis was limited to 114 of the 324 individuals with CD (including 38 with EIMs); while those who have EIMs and ileocolonic disease are likeliest to cycle through more biologic therapies, there is a possibility that using a larger cohort, we would find ileocolonic disease and EIM presence to be independent predictors of biologic cycling. Our subgroup of participants with UC and especially UC and EIMs was small, limiting our findings in the UC group, and it is possible with a larger cohort we would identify aspects of UC such as disease extent which predict EIMs and/or biologic cycling. Our results may be driven by IBD-associated arthritis which was reported as an EIM in the majority of participants, while, EN, uveitis/iritis, PSC, and PG were reported in far fewer. Unfortunately, sub-analyses based on EIM type were not possible due to sample size considerations. Further, we were unable to determine whether the EIMs present were associated with underlying disease activity. As described above, while some EIMs correlate more closely with intestinal disease activity (oligoarticular arthritis, EN, episcleritis) than others EIMs (PSC, ankylosing spondylitis), the small absolute numbers of EIMs in our cohort with the exception of arthritis, were too small to use them as a proxy estimate of whether the increase in EIM-related biologic cycling could be related to an increase in intestinal disease activity. Further, while arthritis was by far the most common EIM, peripheral and axial arthritis were included in the same category. Thus, we were not able to determine if peripheral arthritis, which is more strongly correlated with intestinal disease activity, was the predominant EIM associated with increased biologic cycling. Thus, it is possible that biologic cycling occurred due to persistent disease activity, not from the EIM itself. Nevertheless, we clearly demonstrated that patients with EIM are more likely to utilize biologic therapy regardless of the reason. This information is still useful to clinicians when deciding on starting biologic therapy. Further research is needed to determine why patients with EIM use more biologics than those without. Finally, our choice to perform linear regression, thus limiting models to those with a precise number of biologic exposures available, is both a strength and a limitation. While it resulted in a smaller sample size, the finding of a positive association between EIM and total number of biologics strengthens our results. However, the strengths of this study far outweigh the limitations. The greatest strength of this study is the deep phenotyping and characterization of SPARC participants. Each individual enrolled has extensive information collected not only on disease behavior, phenotype, and location, but previous and current IBD therapies, and history of multiple EIMs. This is done according to a standard protocol, and the entirety of our patient population was seen at 1 center, allowing for less technical variation and fewer site-related confounders. Additionally, the inclusion of both CD and UC patients allowed us to find that EIMs were associated with biologic cycling even when controlling for IBD type.

Conclusions

To our knowledge, we are the first to report that patients with EIMs cycle through more biologics, even after controlling for corticosteroid use, disease duration, diagnosis, age, and sex. Further, we are the first to explore the relationship between ileocolonic CD and EIM development, and their combined association with increased biologic cycling. Given that the jury is still out on the effectiveness of newer biologics for EIMs, and that EIMs frequently require additional therapies or tailored treatment, this finding highlights the need for more research identifying the best ways to maintain remission in patients with EIMs and further exploration of the relationship between EIMs and disease location in those with CD.

Acknowledgments

The results published here are partly based on data from the Study of a Prospective Adult Research Cohort with IBD (SPARC IBD). SPARC IBD is a component of the Crohn's & Colitis Foundation's IBD Plexus data exchange platform. SPARC IBD enrolls patients with an established or new diagnosis of IBD from sites throughout the United States and links

data collected from the electronic health record and study-specific case report forms. Patients also provide blood, stool, and biopsy samples at selected times during follow-up. The design and implementation of the SPARC IBD cohort have been previously described.

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Conflicts of Interest

R.K.C. has received income from consulting and participation in advisory boards for Abbvie, BMS, Fzata, Fresenius Kabi, Janssen, Magellan Health, Sandoz, Samsung Bioepis, Sebela, and Takeda. He has participated in a Data Safety Monitoring Board for Adiso. He is a Member of the Executive Committee for the IBD Education Group and is a Scientific Co-director for the CorEvitas Registry. M.A. and O.A. do not have any conflicts of interest to report.

Data Availability

SPARC data is not yet publicly available. Individual participant data will not be shared.

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