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Inflammatory Bowel Disease in Children With Systemic Juvenile Idiopathic Arthritis

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ABSTRACT. ***Objective.*** The incidence of inflammatory bowel disease (IBD) in juvenile idiopathic arthritis (JIA) is higher than in the general pediatric population. However, reports of IBD in the systemic JIA (sJIA) subtype are limited. We sought to characterize sJIA patients diagnosed with IBD and to identify potential contributing risk factors.

Methods. Using an internationally distributed survey, we identified 16 patients with sJIA who were subsequently diagnosed with IBD (sJIA-IBD cohort). Five hundred twenty-two sJIA patients without IBD were identified from the CARRA Legacy Registry and served as the sJIA-only cohort for comparison. Differences in demographic, clinical characteristics, and therapy were assessed using chi-square test, Fisher exact test, *t*-test, and univariate and multivariate logistic regression, as appropriate.

Results. Of the patients with sJIA-IBD, 75% had a persistent sJIA course and 25% had a history of macrophage activation syndrome. sJIA-IBD subjects were older at sJIA diagnosis, more often non-White, had a higher rate of IBD family history, and were more frequently treated with etanercept or canakinumab compared to sJIA-only subjects. Sixty-nine percent of sJIA-IBD patients successfully discontinued sJIA medications following IBD diagnosis, and sJIA symptoms resolved in 9 of 12 patients treated with tumor necrosis factor-α (TNF-α) inhibitors.

Conclusion. IBD in the setting of sJIA is a rare occurrence. The favorable response of sJIA symptoms to therapeutic TNF-α inhibition suggests that the sJIA-IBD cohort may represent a mechanistically distinct sJIA subgroup. Our study highlights the importance of maintaining a high level of suspicion for IBD when gastrointestinal involvement occurs in patients with sJIA and the likely broad benefit of TNF-α inhibition in those cases.

Key Indexing Terms: autoinflammation, cytokine inhibitors, inflammatory bowel disease, pediatric rheumatology, systemic juvenile idiopathic arthritis

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Systemic juvenile idiopathic arthritis (sJIA) is a chronic inflammatory disease of childhood, observed worldwide. sJIA represents 10–20% of all JIA cases in North America and Europe, where the annual incidence is 0.4–0.9/100,000 and prevalence is 3.5/100,000[1]. sJIA is characterized by the combination of arthritis with a constellation of extraarticular features, including daily fevers, lymphadenopathy, hepatosplenomegaly, serositis (pericarditis and pleuritis), evanescent macular rash, and laboratory evidence of systemic inflammation. In addition to the clinical features unique to this JIA subtype, the genetic architecture of sJIA is distinct from other forms of JIA, even in the ~30% of patients with sJIA who develop persistent polyarthritis[2]. Treatment response also differs in sJIA, with therapeutic interleukin (IL)-1 or IL-6 blockade effective in the majority of patients[3,4,5], whereas other forms of JIA with disease-modifying antirheumatic drug (DMARD)–refractory disease typically improve with tumor necrosis factor-α (TNF-α) inhibition[6]. These findings argue that the pathophysiologic mechanisms driving sJIA significantly diverge from those underlying other forms of JIA.

Among all patients with JIA, more than one-third report chronic gastrointestinal (GI) symptoms without associated bleeding[7]. This relatively common extraarticular complaint has prompted deeper investigation into the significance of such symptoms. Findings thus far indicate that patients with JIA have an increased risk of immune-related GI involvement, including Crohn disease (CD) and ulcerative colitis (UC). Indeed, inflammatory bowel disease (IBD) incidence in patients with JIA, analyzed as a whole, ranges from 20 to > 40 times the IBD rates in the general pediatric population[8,9,10]. However, relatively few patients with sJIA were included in the earlier studies, limiting the ability to perform subgroup analyses focused on sJIA. Thus, it remains unanswered whether the sJIA subtype has a unique relationship with IBD susceptibility. In addition to considering the potential effect of therapeutic IL-1 blockade—a treatment strategy unique to the systemic-onset form of JIA—on IBD development, this relationship is an appealing hypothesis because features of innate immune dysfunction are associated with both sJIA and IBD[11,12,13].

To gain further insight into the relationship between sJIA and IBD, we collected a case series of 16 patients with sJIA who later were diagnosed with IBD. Here, we describe the clinical findings and treatment courses of these patients. Additionally, we compare features of this sJIA-IBD cohort to a larger cohort of sJIA patients without IBD to identify candidate factors associated with IBD in sJIA.

MATERIALS AND METHODS

After approval by our institutional review board (IRB Registration #00006208, protocol #31469), we distributed an online survey to all members of the Childhood Arthritis and Rheumatology Research Alliance (CARRA), a North American network of pediatric rheumatologists, and the international pediatric rheumatology listserv administered by McMaster University in Ontario, Canada. Together these instruments reach a wide, international audience, although the precise number of recipients was not determined in this survey-based study. Sixteen cases of sJIA patients, subsequently diagnosed with IBD between 2004 and 2014, were reported. Diagnoses were assigned by the treating physicians.

Survey respondents provided deidentified data through an online platform (SurveyMonkey; www.surveymonkey.com). Information collected included demographic variables (age at sJIA and IBD diagnoses, sex, ethnicity, and race) and the following clinical data: physical manifestations and laboratory findings at sJIA and IBD presentation, medication regimen and therapy response prior to and following IBD diagnosis, type of IBD as reported by the treating physician based on endoscopic and histopathologic evaluation, family history of IBD in a first- or second-degree relative, sJIA disease activity status (flare or quiescent) within 3 months preceding IBD diagnosis, development of macrophage activation syndrome (MAS) at or following sJIA diagnosis, and type of sJIA course (monocyclic, polycyclic, or persistent; respondents were asked to indicate whether subjects with persistent sJIA had a systemic- or polyarthritis-predominant course).

The cohort identified in this study, termed *sJIA-IBD*, was compared to the CARRA Legacy Registry[14] cohort of sJIA patients without IBD, termed *sJIA-only*. The CARRA Legacy Registry is a convenience registry, enrolling patients at any time during their disease course. The sJIA-only cohort comprised 522 sJIA patients with known age of sJIA onset, who were enrolled in the registry between 2010–2013. The cohort included 150 patients who did not meet the International League Against Rheumatism (ILAR) criteria but were categorized as sJIA by their physician[15]. Three registry patients were excluded from the sJIA-only cohort due to a coexisting diagnosis of IBD.

Statistics. Continuous variables were summarized with mean ± SD and categorical variables presented as frequencies and proportions. To examine the association between categorical demographic, clinical, and treatment variables and IBD in sJIA, we used chi-square test or Fisher exact test for small samples. To compare the age of sJIA onset and illness duration between the 2 groups, we used the *t*-test. Univariate logistic regression with OR and 95% CI was performed to study the relationship between clinical and demographic variables of sJIA-IBD to sJIA-only subjects. Statistically significant variables were then used in multivariate logistic regression modelling to further identify patient characteristics and therapeutics distinguishing the sJIA-IBD cohort from the sJIA-only cohort. All *P* values were 2-sided and statistical significance was defined as $P \leq 0.05$. The data were analyzed with IBM SPSS version 23.

RESULTS

We identified 16 patients with sJIA who subsequently developed IBD (8 female, 8 male). Mean age at sJIA diagnosis was 9.9 ± 3.9

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years (range 1.5–16.1 yrs) and mean age at IBD diagnosis was 12.9 ± 3.2 years (range 7.5–18.8 yrs). Disease characteristics of this sJIA-IBD cohort are shown in Table 1. The most common clinical manifestations at sJIA diagnosis were arthritis (100%), fever (94%), and rash (69%); the latter 2 were specifically attributable to sJIA per the case reporter. Of the sJIA-IBD cohort, 25% experienced MAS, half at the time of sJIA diagnosis and the other half later in the sJIA disease course, but prior to IBD diagnosis. Of the sJIA-IBD patients, 75% had a persistent course of sJIA, with 4 of 12 reporting as persistent systemic and 5 of 12 as persistent arthritic (this information was not available for the other 3 subjects with persistent disease).

The most common clinical features present at IBD diagnosis were diarrhea (75%), abdominal pain (69%), and weight loss (63%). Of the IBD cases, 81% were diagnosed as CD, which is the most common form of IBD across all JIA subtypes[8,9,10]; the remaining patients had indeterminate colitis. C-reactive protein and erythrocyte sedimentation rate were elevated in the majority of patients at both sJIA and IBD diagnoses. No significant differences in the frequency of abnormal laboratory variables were observed at sJIA diagnosis compared to IBD diagnosis. At IBD diagnosis, the mean duration of sJIA was 3 years (SD ± 2.3, range 1.0–9.5 yrs). Within the 3 months prior to IBD diagnosis, 9 patients (56%) were considered to have active sJIA and the remaining 7 had quiescent disease. No respondent reported features suggestive of active systemic disease (e.g., quotidian fever, sJIA rash) at IBD diagnosis, although this was not specifically queried.

We compared treatment regimens of the sJIA-IBD cohort in the 6 months before IBD diagnosis to those used after (Figure 1). Not surprisingly, the frequency of TNF-α inhibitor (TNFi) use significantly increased following IBD diagnosis (5/16 vs 12/16, $P = 0.03$). In the 6 months prior to IBD diagnosis, all 5 patients on therapeutic TNF-α blockade were treated with etanercept [ETN; 1 of these also received adalimumab (ADA)]. In contrast, following IBD diagnosis, all 12 patients treated with TNFi received ADA and/or infliximab (IFX). Nine of these patients were also treated with a conventional DMARD. Of the 8 patients treated with an IL-1 inhibitor prior to IBD diagnosis, only 1 remained on this treatment after IBD was diagnosed ($P = 0.02$). One of the 2 patients treated with tocilizumab (TCZ), an IL-6 inhibitor, remained on this drug following IBD diagnosis.

To identify potential factors influencing the development of IBD among patients with sJIA, we compared the demographic, clinical, and treatment-related features of patients in

Table 1. sJIA- and IBD-related characteristics of the sJIA-IBD cohort (n = 16).

sJIA Features	n (%)	IBD Features	n (%)
Clinical manifestations at sJIA diagnosis		Clinical manifestations at IBD diagnosis	
Arthritis	16 (100)	Diarrhea	12 (75)
Fever attributed to sJIA	15 (94)[a]	Abdominal pain	11 (69)
Rash attributed to sJIA	11 (69)	Weight loss	10 (63)
Lymphadenopathy	4 (25)	Arthritis	8 (50)
Hepato/splenomegaly	3 (19)	Hematochezia	7 (44)
Weight loss	3 (19)	Fever	6 (38)
Serositis	2 (13)	Oral ulcers	2 (13)
Myositis[b]	1 (6)	Perianal disease	2 (13)
Presence of MAS[c]		Failure to thrive	1 (6)
At sJIA diagnosis	2 (13)	Vomiting[b]	1 (6)
During sJIA treatment	2 (13)	Rash attributed to IBD	0 (0)
Course of sJIA disease		Specific IBD diagnosis	
Monocyclic	3 (19)	Crohn disease	13 (81)
Polycyclic	1 (6)	Ulcerative colitis	0 (0)
Persistent	12 (75)[d]	Indeterminate colitis	3 (19)
Laboratory variables		Laboratory variables	
Leukocytosis	9/13 (69)	Leukocytosis	5/15 (33)
Anemia	10/14 (71)	Anemia	9/16 (56)
Thrombocytosis	10/13 (77)	Thrombocytosis	9/15 (60)
Elevated AST and/or ALT	3/12 (25)	Elevated AST and/or ALT	1/14 (7)
Hypoalbuminemia	4/8 (50)	Hypoalbuminemia	8/14 (57)
Elevated ESR	12/12 (100)	Elevated ESR	10/14 (71)
Elevated CRP	12/12 (100)	Elevated CRP	11/15 (73)
Elevated ferritin	8/10 (80)	Elevated stool calprotectin	4/6 (67)

Data on laboratory values were missing for several patients; the denominator for each variable indicates the number of patients for whom a response was provided. Features shown were queried in the survey, except for 2, as noted. [a] One patient had a recent history of fever, which was likely masked by medication at sJIA diagnosis, per the case reporter. [b] Features that were specified as additional features by respondents. [c] No patients developed MAS following IBD diagnosis. [d] Of the subjects with persistent sJIA, 4 were described as systemic-predominant and 5 as polyarthritis-predominant courses, per case reporters who responded to this follow-up question. ALT: alanine aminotransferase; AST: aspartate aminotransferase; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; IBD: inflammatory bowel disease; MAS: macrophage activation syndrome; sJIA: systemic juvenile idiopathic arthritis.

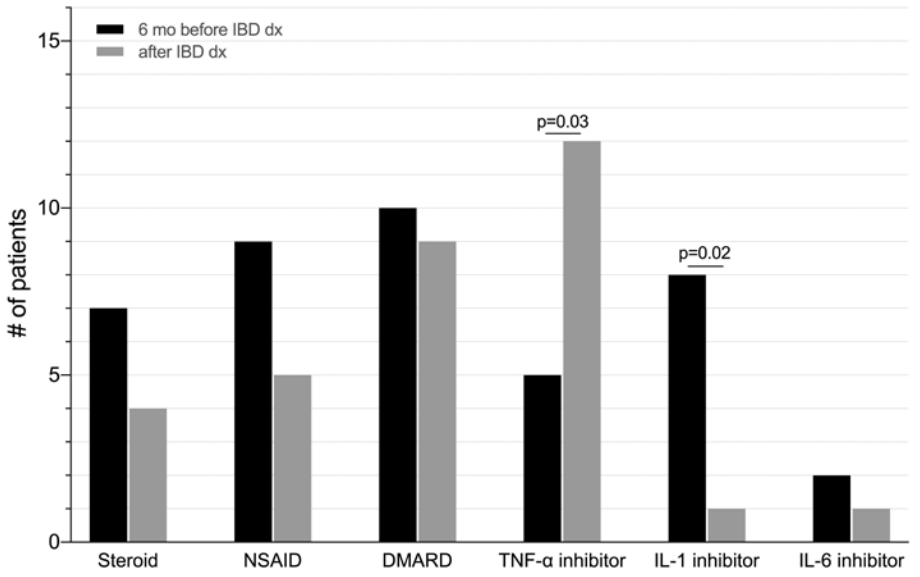

Figure 1. Medication regimens of the sJIA-IBD cohort before and after IBD diagnosis. Bars reflect the number of patients receiving 1 or more class-specific therapy in the 6 months before IBD diagnosis (black) and after (gray). DMARD used before IBD diagnosis included the following (no. patients indicated in parentheses): cyclosporine (1), MTX (7), and tacrolimus (2); DMARD after IBD diagnosis included MTX (5), sulfasalazine (2), and azathioprine (4). TNF-α inhibitors used before IBD diagnosis included ADA (1) and etanercept (5); TNF-α inhibitors after IBD diagnosis included ADA (4) and infliximab (10). IL-1 inhibitors used before IBD diagnosis included anakinra (2) and canakinumab (6); 1 patient remained on canakinumab after IBD diagnosis. IL-6 inhibitor was tocilizumab. Two subjects were treated with mesalamine monotherapy after IBD diagnosis. Regimens in the 6 months before IBD diagnosis do not necessarily reflect medications initiated within this time frame; data on specific timing and duration of therapy were not collected. ADA: adalimumab; DMARD: disease-modifying antirheumatic drug; Dx: diagnosis; IBD: inflammatory bowel disease; IL: interleukin; MTX: methotrexate; NSAID: nonsteroidal antiinflammatory drug; sJIA: systemic juvenile idiopathic arthritis; TNF: tumor necrosis factor.

the sJIA-IBD cohort to a larger sJIA-only cohort (n = 522; see Materials and Methods) from the CARRA Legacy Registry (Table 2). In the sJIA-IBD cohort, the average age at sJIA diagnosis was significantly higher than that in the sJIA-only cohort (9.9 vs 6.0 yrs, $P = 0.0005$). The sex distribution among the 2 cohorts was not significantly different. However, there was a statistically significant difference in racial distribution ($P = 0.007$), most likely reflecting the greater proportion of White patients in the sJIA-only cohort (82%) compared to the sJIA-IBD cohort (44%). There was no significant difference between the groups in terms of ethnicity or clinical manifestations at sJIA diagnosis. However, significantly more patients in the sJIA-IBD cohort had a family history of IBD compared to the sJIA-only cohort (19% vs 0.8%, $P = 0.001$).

Table 2 also lists the medications used to treat sJIA any time in the disease course prior to IBD diagnosis. Relative to the sJIA-only cohort, we identified statistically significant differences in the proportion of patients treated with NSAID, tacrolimus, and canakinumab. Of the sJIA-IBD cohort, 25% received TCZ compared to 10% in the sJIA-only cohort, but this difference did not reach statistical significance ($P = 0.07$).

To further identify candidate factors associated with the development of IBD in sJIA, we compared the sJIA-only and sJIA-IBD cohorts using multivariate logistic regression modeling. As shown in Table 3, this approach revealed that older age at sJIA diagnosis, family history of IBD, non-White origin, treatment with ETN, and treatment with canakinumab were all statistically significant risk factors for IBD in patients with sJIA.

sJIA-IBD subjects were followed for a median of 2.3 years (range 1–6 yrs), and all 16 patients were followed for at least 1 year, after IBD diagnosis. One (6%) had concurrent flares of sJIA and IBD, 3 (19%) experienced sJIA flare while IBD was quiescent, and 8 (50%) had IBD flare while sJIA was quiescent. Four patients (25%) maintained quiescence of both diseases; all of these received a monoclonal antibody TNFi, and remained off sJIA-specific therapy, after IBD was diagnosed. Eleven subjects (69%) were able to stop sJIA treatment after IBD diagnosis, and only 2 of these experienced a subsequent sJIA flare (1 while IBD was quiescent and the other with an IBD flare). The 1 patient who remained on IL-1 inhibition after IBD diagnosis maintained sJIA quiescence but experienced an IBD flare on sulfasalazine; this resolved with addition of oral steroids to the treatment regimen. Overall, sJIA activity did not closely correlate with IBD onset or flare, or with discontinuation of IL-1 inhibitors. Interestingly, however, respondents noted that sJIA symptoms were effectively treated in 9 of 12 (75%) patients whose IBD was treated with monoclonal antibody TNFi (data not shown).

DISCUSSION

Here we present 16 patients with sJIA who subsequently

Table 2. Comparison of sJIA-IBD cohort (n = 16) with sJIA-only cohort (n = 522).

Characteristic	sJIA-IBD, % of Cohort	sJIA-only, % of Cohort	*P*
Age of sJIA onset, yrs			
Mean ± SD	9.9 ± 3.9	6.0 ± 4.4	0.0005
Age range	1.5–16.1	0.2–16.6	
Mean disease duration	3.0 ± 2.3	4.6 ± 4.2	NS
Sex			NS
Female	8 (50)	295 (57)	
Male	8 (50)	227 (43)	
Race			0.007
White	7 (44)	425 (82)	
Black	2 (13)	54 (10)	
Native American	0 (0)	5 (1)	
Asian	2 (13)	18 (4)	
Hawaiian/Pacific Islander	0 (0)	1 (0.2)	
Other	3 (19)	14 (3)	
Unknown	2 (13)	5 (1)	
Ethnicity			NS
Hispanic	1 (6)	70 (13)	
Non-Hispanic	15 (94)	452 (87)	
Family history of IBD	3 (19)	4 (0.8)	0.001
Treatment history[a]			
Steroids	13 (81)	441 (85)	NS
NSAID	13 (81)	252 (48)	0.01
Methotrexate	10 (63)	365 (70)	NS
Tacrolimus	2 (13)	8 (2)	0.03
Cyclosporine	2 (13)	51 (10)	NS
Tocilizumab	4 (25)	51 (10)	NS
≥ 1 TNF-α inhibitor[b]	8 (50)	195 (37)	NS
Adalimumab	3 (19)	58 (11)	NS
Etanercept	6 (38)	150 (29)	NS
Infliximab	3 (19)	61 (12)	NS
≥ 1 IL-1 inhibitor[a]	10 (63)	203 (39)	NS
Anakinra	8 (50)	197 (38)	NS
Canakinumab	6 (38)	13 (2)	< 0.0001

[a] Treatment history includes medications used at any time in sJIA course (prior to IBD diagnosis for sJIA-IBD subjects). [b] Number of patients who received ≥ 1 class-specific biologic. IBD: inflammatory bowel disease; IL: interleukin; NS: not significant ($P > 0.05$); NSAID: nonsteroidal antiinflammatory drug; sJIA: systemic juvenile idiopathic arthritis; TNF: tumor necrosis factor.

Table 3. Risk factors for development of IBD in patients with sJIA: comparison of sJIA-IBD and sJIA-only cohorts.

	OR	95% CI	*P*
Older age at sJIA diagnosis	1.26	1.07–1.48	0.007
Non-White origin	5.52	1.29–23.62	0.02
Family history of IBD	108.39	11.88–988.91	< 0.0001
Etanercept	5.49	1.13–26.63	0.035
Canakinumab	217.22	27.92–1689.74	< 0.0001

IBD: inflammatory bowel disease; sJIA: systemic juvenile idiopathic arthritis.

developed IBD. To our knowledge, this is the largest case series to date describing IBD in sJIA. In the only other case series examining IBD specifically in sJIA, IBD was diagnosed in 3 of 82 sJIA patients at a single center[16]. Two of the 3 patients had CD, which is comparable to our cohort (81% CD) and the predominant pathology observed in other studies of IBD in JIA. Notably, IBD-related arthritis is twice as likely in CD compared to UC[17]. Also similar to our cohort, the 3 sJIA patients in the single-center cohort were older at sJIA diagnosis (with mean age 12.5 yrs) compared to the more common younger age of sJIA onset[18,19]. Interestingly, the majority of childhood-onset IBD is diagnosed in adolescence[20]. Significantly fewer patients in the sJIA-IBD cohort were White compared to the sJIA-only cohort. Overall, for the variables we collected, the demographic features of the sJIA-IBD cohort are similar to IBD worldwide[21]. In the sJIA-IBD cohort, 19% had a family history of IBD, which was significantly higher than in the sJIA-only cohort, and consistent with prior reports that up to 20% of pediatric patients with IBD have an affected relative[20].

Our study revealed several other factors that may contribute to the risk of IBD in sJIA. Comparisons with the sJIA-only cohort found that ETN treatment was associated with a

significantly higher risk of IBD (OR 5.49, 95% CI 1.13–26.63, $P = 0.035$; Table 3). This is consistent with prior reports that have implicated ETN as a risk factor for IBD in patients with all JIA subtypes[8,9,10]. Similarly, in a nationwide cohort study of Danish patients with various autoimmune diseases, including rheumatoid arthritis, psoriasis, and psoriatic arthritis, investigators found that patients treated with ETN, but not ADA or IFX, had an increased risk of developing IBD during treatment[22]. We suspect that physicians treating the sJIA-IBD subjects recognized this ETN-specific association with IBD: Prior to IBD diagnosis, the majority (75%) of patients treated with TNFi received ETN. Once IBD diagnosis was established, however, either ADA or IFX was chosen for 12/12 patients receiving TNFi. The strong association of ETN, but not the other TNFi, with IBD development may be explained by the fact that TNFi differ in their physiologic effects. ADA and IFX induce apoptosis in lamina propria T cells, whereas ETN does not. In contrast, only ETN can bind to and prolong the half-life of circulating TNF-α and can also increase levels of interferon γ (IFN-γ)[23,24,25].

More sJIA-IBD subjects were treated with IL-1 inhibitors compared to sJIA-only subjects (63% vs 39%, $P = 0.07$). This trend raises the possibility that therapeutic IL-1 blockade contributes to IBD development in sJIA. Our data show a statistically significant association of canakinumab and IBD in sJIA (OR 217.22, 95% CI 27.92–1689.74, $P < 0.0001$), although not with anakinra. However, in the other case series describing IBD in sJIA, all 3 patients were receiving IL-1 inhibitors (2 with anakinra and 1 with canakinumab) when IBD symptoms developed[16]. In a randomized clinical trial comparing response to 1-month anakinra treatment versus placebo (n = 12 sJIA patients per group), 1 patient in the anakinra treatment arm developed CD[26]. Interestingly, IL-1 is thought to contribute to IBD pathogenesis. High levels of IL-1 are found in biopsies of IBD patients, and serum levels of the endogenous IL-1 inhibitor, IL-1RA, are elevated in patients with active IBD[27]. A recent study demonstrated that IL-1RA–deficient mice, with elevated levels of IL-1α and IL-1β, spontaneously developed histologic features of IBD[28]. A possible explanation for these apparent contradictions is that, in animal models of IBD, IL-1α and IL-1β play opposing roles, with IL-1α acting in a proinflammatory fashion, and IL-1β promoting healing and repair of colonic tissue[29]. Anakinra, a recombinant form of IL-1RA, blocks the activity of both IL-1α and IL-1β, whereas canakinumab is a monoclonal antibody specifically targeting IL-1β. It is possible that either of these medications may alter the IL-1 signaling equilibrium required to maintain immune homeostasis within the gut.

The evolution of sJIA over time to a Th17-driven disease[30,31] may also contribute to IBD development[16], because Th17 cells are implicated in IBD[32]. In a recent comparative analysis of gene regulation between IBD and JIA subtypes (sJIA, oligoarticular and polyarticular JIA), IBD most closely resembled sJIA[12]. Patients with sJIA, UC, and CD significantly upregulated innate immunity gene expression compared to the other JIA subtypes, based on RNA-Seq analysis of whole blood. A rare mutation in *LACC1*, which encodes a central metabolic regulator for macrophages and other immune cells[33,34], was initially identified in monogenic forms of early-onset CD[35] and was later described in 5 consanguineous families with monogenic sJIA-like disease[36]. Interestingly, LACC1 downregulates TNF and IL-17 production in mouse models of arthritis and inflammation, and *LACC1*-deficient mice have more severe colonic lesions compared to their wild-type counterparts[37]. Further, in multiple studies, *LACC1* single-nucleotide polymorphisms represent strong genetic risk factors for CD, UC, and both systemic and nonsystemic forms of JIA[38,39,40,41].

Another possible biological overlap between sJIA and IBD in a subset of sJIA-IBD patients involves IFN-γ. Of the sJIA-IBD cohort, 25% had a history of overt MAS, a possible enrichment over the ~10% incidence of MAS reported in patients with sJIA[42,43]. Serum levels of IFN-γ and CXCL9, an IFN-γ–induced chemokine, are elevated in sJIA patients with MAS compared to sJIA patients without MAS[44], and IFN-γ is also strongly implicated in IBD pathogenesis[24,25].

Interestingly, sJIA symptoms resolved in 75% of the 12 sJIA-IBD subjects treated with TNFi for their IBD. This was an unexpected finding, because these medications do not typically confer improvement in sJIA[45]. However, one study found that in the small proportion of sJIA patients who favorably responded to anti-TNF therapy, 11/45 (24%) of the subjects studied had significantly less frequent systemic involvement at treatment initiation compared to the patients who did not achieve remission (18% vs 56%, $P = 0.03$)[46]. In the sJIA-IBD cohort, 5 of 7 subjects discontinued IL-1 inhibition without sJIA flare, and no subject had an episode of MAS after IBD diagnosis. Of the sJIA-IBD subjects, 75% had a persistent sJIA course, which is higher than the ~40% in reported sJIA cohorts[15,47,48]. Though we were unable to ascertain further details for 3 of the 12 subjects with a persistent sJIA course, the collective data suggest relatively lower systemic disease activity in the sJIA-IBD cohort compared to patients with systemic feature–prominent sJIA. Taken together with the development of IBD, these findings suggest unique biology in the sJIA-IBD cohort, possibly more akin to the chronic polyarthritis subset of sJIA patients[48], though clearly not as common[15]. An alternative possibility is that sJIA-IBD subjects had a primary diagnosis of IBD that was initially misdiagnosed as sJIA, due to predominance of extraintestinal features and minimal GI complaints. Indeed, 22% of pediatric IBD patients do present with extraintestinal complaints, such as arthritis and anemia, as the main initial features[20,49]. However, arguing against this possibility, fever and rash, which have unique characteristics in sJIA[50], were described in 100% and 69% of the sJIA-IBD cohort, respectively, and were specifically attributed to sJIA at disease onset by case reporters.

There are several limitations to our study. The study is retrospective with small numbers. We did not collect data on timing or duration of therapy. These gaps in information limit our ability to analyze how these variables may influence susceptibility to IBD. However, in prior studies of IBD in JIA, therapy duration did not strongly correlate with IBD onset[8,9,10,16]. The sJIA and IBD diagnoses were based on physician judgement, and our survey did not require that patients meet ILAR criteria for sJIA. The CARRA Legacy Registry included 150 patients who

did not meet ILAR criteria but were categorized as sJIA by their physician[15]. To be consistent in our comparisons, we included these subjects (together with 372 who met ILAR criteria) in the sJIA-only cohort. The CARRA Legacy sJIA-only cohort also matches our sJIA-IBD cohort for the time period during which cases occurred, providing a suitable group for comparison of medication use.

The true incidence of IBD in sJIA, and whether this incidence changes as sJIA treatment approaches evolve, will be of interest to determine. This information will have implications for the role of particular medications as triggers or contributors to pathogenesis. More work is also needed to better understand the biologic relationship between IBD and sJIA. More detailed clinical characterization, immunophenotyping, genetics, and responses to particular therapies may all shed light on this question.

Since ETN is associated with IBD development in all forms of JIA, preferential use of ADA or IFX for active arthritis may be a prudent approach in patients with JIA, especially for those with a family history of IBD. For sJIA patients who develop biopsy-proven IBD, a suggested strategy is the discontinuation of IL-1 inhibitors and/or ETN, consideration of treatment with other TNFi, and early collaboration with a gastroenterology specialist. Our findings on risk factors for IBD in patients with sJIA will require confirmation in future studies, particularly as the size differences between the 2 cohorts limited the extent to which the OR could be precisely determined. Nonetheless, our study highlights the importance of maintaining a high level of suspicion in sJIA patients with GI symptoms so as not to miss the possibility of IBD.

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