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Determinants of Tumor Necrosis Factor Inhibitor Use in Juvenile Spondyloarthropathy and Impact on Clinical Disease Outcomes

Melissa Oliver, Julia F. Simard, Tzielan Lee, Dana Gerstbacher, and Christy Sandborg

Objective. The objectives of this study were to characterize the reasons for tumor necrosis factor inhibitor (TNFi) initiation in patients with juvenile spondyloarthropathy (JSpA) and identify clinical correlates and to assess the effect of TNFi therapy on JSpA disease activity.

Methods. We conducted a retrospective cohort study of 86 patients with JSpA with first-time use of a TNFi over a 7-year period at Stanford Children's Health. We assessed the physician's reason for TNFi initiation, disease activity at 6 months, and clinical disease status at 12 months following TNFi start. Changes in active joint count, enthesitis count, and pain were measured. Demographics, physician reasons for TNFi initiation, and clinical characteristics were summarized.

Results. The mean age at JSpA diagnosis was 12.4 years (SD 4.0 years), and the mean time from diagnosis to TNFi initiation was 1.6 years (SD 2.3 years). The most common reason for initiating a TNFi was active disease on physical examination (61%). At 6 months post TNFi initiation, patients on average had three fewer active joints and one fewer active enthesitis point. Patient-reported pain improved from moderate/severe to mild. After 12 months, 54% of patients had active disease.

Conclusion. The physician's decision to initiate a TNFi relied mostly on physical examination findings. Despite improvement in arthritis, enthesitis, and patient-reported pain at 6 months post TNFi initiation, the majority of the patients still had active disease after 1 year of therapy.

INTRODUCTION

Juvenile idiopathic arthritis (JIA) is one of the most common chronic childhood diseases seen by pediatric rheumatologists. The prevalence of JIA varies between 16 and 150 per 100 000 (1). The juvenile spondyloarthropathy (JSpA) subtype accounts for up to 20% of all cases of JIA (2,3). When compared with other JIA subtypes, patients with JSpA have higher disability and pain scores, as well as worse function, poorer quality of life, and lower rates of clinical remission (4). The characteristic features of JSpA differ from other JIA subtypes and include enthesitis, dactylitis, HLA antigen B27 positivity, inflammatory back pain, acute anterior uveitis, and sacroiliitis. Some clinical parameters that assess active disease, such as inflammatory back pain or entheseal tenderness, can be challenging to measure without imaging. Additionally, some children may have silent sacroiliitis (5). Sacroiliitis and enthesitis predict poor prognosis in JSpA, and it is important that, when assessing disease activity, these are taken into account (4,6). These disease-specific features are generally not included in many JIA clinical disease assessments, with the exception of the Juvenile Spondyloarthritis Disease Activity Index (JSpADA), which is a composite clinical disease activity score that has been retrospectively validated (7).

In the biologic era, long-term follow-up studies of more than 15 years have shown that only 20% to 37% of patients with JSpA achieved clinical remission while off medication (8,9). Biologics, such as tumor necrosis factor inhibitors (TNFi), produce clinical improvements in numerous rheumatic diseases, including adult ankylosing spondylitis, and are increasingly being used for pediatric inflammatory arthritis (10,11). In patients with JSpA, TNFi induced clinical remission after 6 months in one observational study and decreased disease activity measures in a double-blind randomized controlled trial of enthesitis-related arthritis (ERA) (12,13). Despite their efficacy, some studies showed that

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Melissa Oliver, MD, MS (current address: Indiana University, Indianapolis, Indiana), Julia F. Simard, ScD, Tzielan Lee, MD, Dana Gerstbacher, MD, Christy Sandborg, MD: Stanford University, Stanford, California.
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Address correspondence to Melissa Oliver, MD, MS, Indiana University, CL200, 1120 West Michigan Street, Indianapolis, IN 46202. Email: msoliver@iu.edu.
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pediatric patients did not start a TNFi until 2 to 3 years after disease onset. In these instances, however, they were typically started for worsening disease activity, failure to respond to prior treatments, or new radiographic findings, which is typically a late disease finding (10,14–16). TNFi are indicated for sacroiliitis with inadequate nonsteroidal antiinflammatory drug (NSAID) response, but disease-modifying antirheumatic drugs (DMARDs) remain first line for peripheral disease following an NSAID trial (17).

Because JSpA is typically more challenging to manage than other subtypes of JIA and because TNFi therapy is not considered first line unless there is advanced disease or evidence of sacroiliitis, we aim to gain insight on TNFi usage in this particular patient population. By examining the factors that influence a physician's decision to escalate therapy to a TNFi in patients with JSpA, such as physical examination or imaging findings or pain, we can highlight areas for improvement in disease management and potentially identify a specific or earlier role for their use. We evaluated the reasons for escalating to TNFi therapy in a JSpA population and assessed whether there were specific disease characteristics or factors that influenced the decision. Our study characterizes the reasons for TNFi initiation in patients with JSpA and the effect of TNFi therapy on clinical disease activity.

MATERIALS AND METHODS

Patient population. Patients with JSpA who initiated their first TNFi between 2007 and 2014 were identified retrospectively from the Pediatric Rheumatology Department at Stanford Children's Health using *International Classification of Diseases, Ninth Revision* (ICD-9) codes and confirmed by the primary author (MO). Patients with a diagnosis of JSpA were included if they were 16 years or younger at the time of diagnosis; had any of the following subtypes: ERA, psoriatic arthritis (PsA), undifferentiated spondyloarthritis (USpA), juvenile ankylosing spondylitis (JAS), reactive arthritis, and arthritis associated with inflammatory bowel disease (IBD); and were prescribed TNFi therapy (etanercept, adalimumab or infliximab) for the first time during the study period. JSpA subtype diagnoses were defined as meeting criteria for the International League of Associations for Rheumatology (ILAR) criteria for ERA, USpA, and PsA (18). For JAS, the diagnosis was adapted from the ILAR criteria for ERA, and patients had to have imaging confirmation, either by x-ray or magnetic resonance imaging (MRI), of sacroiliitis. Arthritis associated with IBD is not included in the ILAR criteria, so for this study, it was defined as enthesitis or arthritis for greater than 6 weeks associated with IBD. Exclusion criteria included patients starting a TNFi for indications other than treatment of arthritis or enthesitis, eg, active or worsening IBD or chronic uveitis. Patients with any history of prior TNFi use or use of other biologic DMARDs were also excluded. This study was approved by the Stanford University Institutional Review Board (protocol No. 36088).

Data collection and study variables. Data were collected from four study time points: 1) JSpA diagnosis, 2) TNFi initiation, 3) 6 months post TNFi initiation, and 4) 12 months post TNFi initiation. The physician's reason for TNFi initiation was determined on the basis of the primary rheumatologist's clinical documentation of physical examination and imaging findings and assessment of the patient and was categorized into physical examination findings of active disease alone, image findings of active disease alone, both physical examination and imaging findings, and/or pain. The primary author (MO) reviewed all clinical documentation and the assessment and plans for each patient at each study time point. Documented imaging findings were confirmed with radiology reports. Additional data collected included age, race and ethnicity, sex, date of diagnosis, disease subtype, radiographic imaging studies (such as x-rays, ultrasounds, and MRI reports), HLA antigen B27 status, TNFi type, TNFi start and stop dates, concomitant medications, inflammatory markers (erythrocyte sedimentation rate and C-reactive protein level), physical examination findings, presence of uveitis, patient-reported morning stiffness, pain score on a visual analog scale (VAS), and patient verbally reported description of pain at each time point. Imaging was cross-checked with the radiology records. For patients who delayed their TNFi medication start after it was recommended by their physician, their start date was recorded as the actual date they started the medication and not when it was prescribed.

Pain on a VAS was not documented for every patient, but the patient's verbally reported pain was well documented in the interval history; thus, an imputed categorical pain variable was used as a surrogate for the pain VAS score. This was derived from an expert consensus from a group of pediatric rheumatologists (MO, TL, DG, CS) who reviewed the documentation of patients' verbally reported pain in the clinic notes from a sample of 10 patients. Pain was categorized by specific descriptors and correlated with three levels of a verbal rating pain scale: 1) none, 2) mild, or 3) moderate/severe pain. For example, if the patient reported no pain, that was categorized as none; if the patient reported some pain or pain a couple days a week, that was categorized as mild; or if the patient reported significant pain or pain on most days, that was categorized as moderate/severe. The clinical disease status (ie, active, inactive, clinical remission while on or off medications) at 12 months post TNFi initiation was derived from the clinical documentation and determined by one pediatric rheumatologist (MO). Four pediatric rheumatologists performed an internal validation study on the clinical disease status at 12 months post TNFi initiation in eight patients. Cohen's κ coefficient was used to assess the interrater agreement for 12-month clinical disease activity status, and there was an observed high level of agreement among the multiple raters ($\kappa = 0.86$). The primary author (MO) surveyed the physicians in the Pediatric Rheumatology Department at Stanford Children's Health regarding their practices on documenting physical examination

findings at clinic visits, specifically their joint and enthesitis examination techniques. All physicians had been trained at Stanford Children's Health and had a similar physical examination technique for assessing joint count and enthesitis. Duration of disease at TNFi initiation was defined as the time from JSpA diagnosis to the date the physician initiated a prescription of a TNFi. This was categorized as: less than or equal to 1 month, greater than 1 to 6 months, and greater than 6 months. Study data were collected and managed by using REDCap, hosted at the Stanford Center for Clinical Informatics (19).

Exposure. Exposure was the initiation of a TNFi therapy (etanercept, adalimumab, or infliximab) based on the physician's documentation of their recommendation to start a TNFi in the patient medical record and/or whether the medical reconciliation listed the medication.

Outcomes. Outcomes of interest were the physician's reason for TNFi initiation and the improvement in disease activity after TNFi initiation. Disease activity was assessed by using the active joint count, the active enthesitis count, and the imputed pain variable. These were calculated at the four study time points, and the change between TNFi initiation and 6 months post TNFi initiation was the primary outcome. The clinical disease activity status at 12 months after TNFi initiation was also assessed as a secondary outcome and measured as 1) active disease, 2) inactive disease, 3) clinical remission while on medication, or 4) clinical remission while off medications, according to the Wallace criteria for clinical inactive disease (20).

Statistical analysis. Baseline patient demographics, physician's reason for TNFi initiation, and clinical characteristics at TNFi initiation were summarized by using descriptive statistics. At 6 months post TNFi initiation, median changes in active joint and enthesitis counts and the median change in the imputed pain variable were measured. The clinical disease status at 12 months post TNFi initiation was measured by using descriptive statistics. We compared median changes in active joint and enthesitis counts by physician's reason for TNFi initiation and by disease duration at TNFi start. Similarly, we compared the 12-month clinical disease status by physician's reason for TNFi initiation and by disease duration at TNFi start. Additionally, JSpA clinical characteristics at diagnosis and at TNFi initiation were compared with the 12-month clinical disease status. Nonparametric measures were used because of the small sample size. Between-group comparisons were made by using the Kruskal-Wallis test for continuous outcomes and Fisher's exact test for categorical outcomes. Comparisons made within two groups used the Wilcoxon signed rank test for changes in joint and enthesitis counts and analysis of median scores for change in pain score. Statistical analysis was performed on SAS software v9.4 (SAS Institute, Inc).

RESULTS

Baseline demographics. There were 101 patients who met initial inclusion criteria (a JSpA ICD-9 code and TNFi exposure). Fifteen patients were excluded from the final analysis because they did not have clinical documentation from all three of the study time points (ie, TNFi initiation, 6 months after initiation, and 12 months after initiation). A total of 86 patients had clinical documentation available at JSpA diagnosis, TNFi initiation, and 6 months post TNFi initiation. Of those 86 patients, 80 had clinical documentation available at 12 months after TNFi initiation, and these patients were used to assess the 12-month clinical disease activity status.

Baseline characteristics and demographics are summarized in Table 1. The mean age at JSpA diagnosis was 12.4 years (SD 4.0 years). The mean age at TNFi initiation was 14.0 years (SD 3.5 years), and the mean time from JSpA diagnosis to start of a TNFi was 1.6 years (SD 2.3 years). Of patients, 11.6% started a TNFi within 1 month of being diagnosed with JSpA, 41.9% started a TNFi greater than 1 to 6 months after being diagnosed with JSpA, and 46.5% started a TNFi more than 6 months after being diagnosed with JSpA. Approximately 63% had abnormal imaging findings suggestive of active disease prior to starting TNFi therapy. Sacroiliitis or bone erosions, both indicators for starting a TNFi sooner, were noted on imaging in 49% of all patients. Most patients were still on TNFi therapy 12 months after starting (85%). No TNFi discontinuations were due to inactive disease.

Table 1. Baseline characteristics and demographics (N = 86)

	Value
Mean age at JSpA diagnosis (SD), y	12.4 (4.0)
Mean age at TNFi start (SD), y	14.0 (3.5)
Male sex, n (%)	48 (55.8)
Race, White, n (%)	49 (57.0)
JSpA subtype, n (%)	
Enthesitis-related arthritis	33 (38.4)
Juvenile ankylosing spondylitis	26 (30.2)
Psoriatic arthritis	15 (17.4)
Arthritis associated with IBD	8 (9.3)
Undifferentiated spondyloarthritis	4 (4.7)
HLA antigen B27–positive, n (%)	33 (38.4)[a]
Sacroiliitis/bone erosions on imaging prior to TNFi start, n (%)	37 (48.7)
Prior JSpA treatment, n (%)	
NSAIDs	81 (94.2)
DMARDs	60 (69.8)
Steroids, oral	39 (45.4)
Steroids, intraarticular	20 (23.5)
Prescription pain medicine	10 (11.6)
First TNFi prescribed, n (%)	
Etanercept	74 (86.1)
Adalimumab	8 (9.3)
Infliximab	4 (4.6)

Abbreviations: DMARD, disease-modifying antirheumatic drug; IBD, inflammatory bowel disease; JSpA, juvenile spondyloarthropathy; NSAID, nonsteroidal antiinflammatory drug; TNFi, tumor necrosis factor inhibitor.
[a] Sixteen (18.6%) had unknown HLA antigen B27 positivity (included in the denominator).

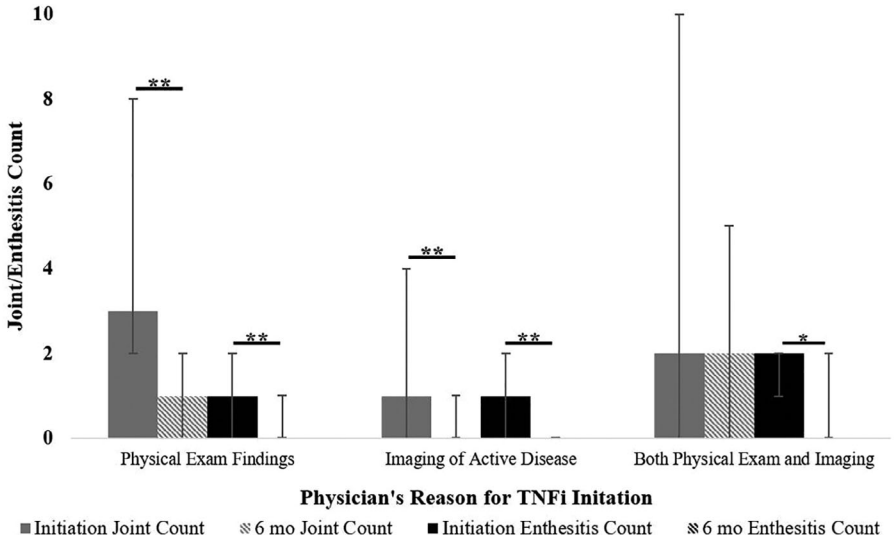

Figure 1. Median joint and enthesitis counts at tumor necrosis factor inhibitor (TNFi) initiation and at 6 months, by physician's reason for initiation. *$P < 0.01$; **$P < 0.001$.

Reason for TNFi initiation. The most common physician reason for TNFi initiation was physical examination findings of active disease alone (61%), followed by abnormal imaging findings alone (24%) and both physical examination and abnormal imaging findings (14%). One patient initiated TNFi therapy because of intolerance to methotrexate. Pain was included as a reason for TNFi initiation in 23% of patients, but pain was never the only reason for initiation, nor was it found in combination with abnormal imaging findings as a reason for initiation.

The physician's reason for TNFi initiation differed among the JSpA subtypes. Compared with other subtypes, more patients with ERA and PsA subtypes started a TNFi for physical examination findings alone, and more patients with JAS started a TNFi for imaging findings alone ($P < 0.0001$).

Clinical outcome at 6 months. The median active joint count at TNFi initiation was 2 (interquartile range [IQR] 1-7), and at 6 months, it decreased to 1 (IQR 0-2). The median active enthesitis count at TNFi initiation was 1 (IQR 0-2), and at 6 months, it was 0 (IQR 0-1). There was also an improvement seen in pain after the first 6 months of treatment, which went from moderate/severe pain to mild pain.

The median joint and enthesitis counts at TNFi initiation and 6 months post TNFi initiation varied by physician's reason for

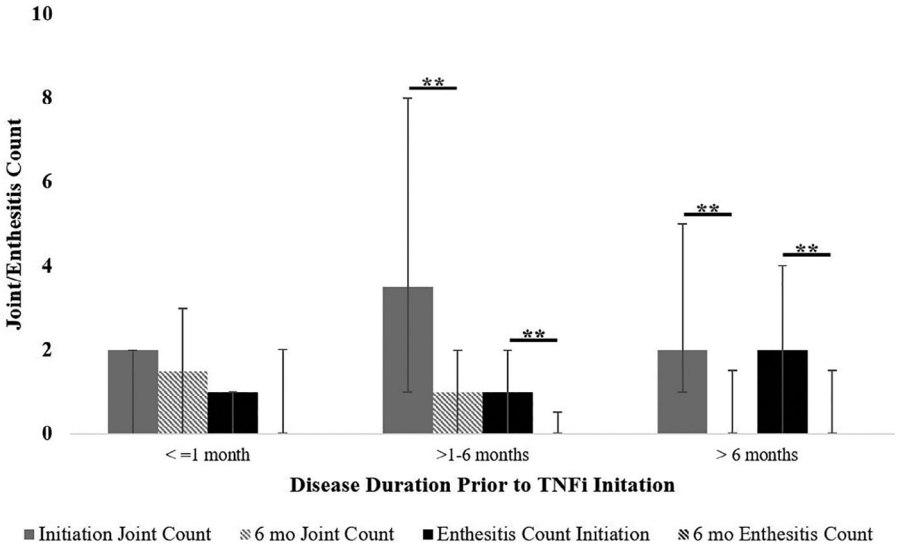

Figure 2. Median joint and enthesitis counts at tumor necrosis factor inhibitor (TNFi) initiation and at 6 months, by disease duration. **$P < 0.001$.

Table 2. Clinical disease status at 12 mo, grouped by the physician's reason for TNFi initiation (n = 80[a])

	Clinical disease status at 12 mo, n (%)		
Reason for physician-initiated TNFi	Active	Inactive	Clinical remission on medication
Physical examination findings	26 (55.3)	11 (23.4)	10 (21.3)
Imaging of active disease	9 (43.0)	8 (38.0)	4 (19.0)
Both physical examination and imaging findings	8 (66.7)	4 (33.3)	0 (0)

Abbreviation: TNFi, tumor necrosis factor inhibitor.
[a] n = 80 (number of patients with a 6-mo follow-up who also had a 12-mo follow-up).

Table 3. Clinical disease status at 12 mo, grouped by the disease duration prior to TNFi (n = 80[a])

	Clinical disease status at 12 mo, n (%)		
Disease duration prior to TNFi	Active	Inactive	Clinical remission on medication
≤1 mo	5 (55.6)	2 (22.2)	2 (22.2)
>1-6 mo	16 (50.0)	10 (31.2)	6 (18.8)
>6 mo	22 (56.4)	11 (28.2)	6 (15.4)

Abbreviation: TNFi, tumor necrosis factor inhibitor.
[a] n = 80 (number of patients with a 6-mo follow-up who also had a 12-mo follow-up).

TNFi initiation (Figure 1) and by disease duration prior to TNFi initiation (Figure 2). The greatest improvement in active joint count was observed in the physical examination findings alone group compared with the other physician's reason groups ($P < 0.0001$). The active enthesitis count also decreased in each of the physician's reason groups, although this observed decrease was not as large as that for the active joint count. The patients with a disease duration of greater than 1 month at the start of a TNFi demonstrated the largest decrease in their active joint counts compared with the group who started a TNFi within 1 month of diagnosis. Active enthesitis counts also decreased, with the exception of those who started a TNFi within 1 month.

Patients who had active disease on radiographic imaging prior to initiating a TNFi did not differ from patients who had normal imaging findings regarding clinical characteristics and laboratory measures after 6 months of TNFi therapy.

Clinical outcome at 12 months. Of the 80 patients who had clinical documentation available at 12 months after TNFi initiation, 53.8% were considered to still have active disease, 28.8% had inactive disease, and 17.5% were in clinical remission on medications. Table 2 shows the 12-month clinical disease status by the physician's reason for TNFi initiation, and Table 3 shows the 12-month clinical disease status by the disease duration at TNFi start. Although there was a slightly higher proportion of patients with active disease after 1 year of TNFi therapy compared with those with inactive disease and clinical remission, this was not statistically significant for either the physician's reason for TNFi initiation or the disease duration ($P = 0.38$ and 0.95, respectively).

The initial joint and enthesitis counts at diagnosis and TNFi initiation are shown in Table 4. Patients who were in clinical remission at 12 months post TNFi initiation had a lower enthesitis count at the time of JSpA diagnosis and at the time of TNFi initiation compared with those who still had active disease or inactive

Table 4. Initial joint and enthesitis counts and corresponding to 12-mo clinical disease status (n = 80[a])

	Clinical disease status at 12 mo			
	Active	Inactive	Clinical remission on medication	*P* value
At JSpA diagnosis				
Joint count, median (IQR)	2 (0-5)	2 (1-4)	2 (2-5)	0.27
Enthesitis count, median (IQR)	2 (0-2)	2 (0-2)	0 (0-1)	0.66
At TNFi initiation				
Joint count, median (IQR)	2 (0-6)	3.5 (1-10)	3 (2-5)	0.51
Enthesitis count, median (IQR)	1 (0-2)	2 (0-2)	0 (0-0)	0.0044

Abbreviations: IQR, interquartile range; JSpA, juvenile spondyloarthropathy; TNFi, tumor necrosis factor inhibitor.
[a] n = 80 (number of patients with a 6-mo follow-up who also had a 12-mo follow-up).

disease ($P = 0.0044$). There were no other differences in the clinical characteristics found at the time of diagnosis of JSpA or TNFi initiation when compared with the 12-month clinical disease status. Furthermore, there were no associations noted between the JSpA subtypes or HLA antigen B27 status and the 12-month clinical disease status.

DISCUSSION

Our study explored the relationship between TNFi initiation and clinical disease activity in patients with JSpA at one center. We found that the majority of physicians escalated therapy in patients with JSpA to a TNFi solely because of physical examination findings, and there was an improvement in their active joint counts, active enthesitis counts, and patient-reported pain at 6 months post TNFi initiation. However, many of the patients still had active disease 1 year after starting a TNFi.

When compared with other JSpA cohorts, our study population was similar regarding age at JSpA diagnosis, age at start of a TNFi, and sex. These prior cohorts were also predominantly male (60%-80%) and had a similar average age at diagnosis and start of TNFi, which ranged from 11 to 13 years and 14 to 15 years, respectively (12,13,21). In our cohort, ERA was the most common subtype. Of the patients who had a documented HLA antigen B27 test result, the percentage of patients who were HLA antigen B27–positive in our cohort was smaller (38%) when compared with the other cohorts. However, another study suggested the prevalence may be closer to 50% in the pediatric population (21), and a more recent study reported a similar HLA antigen B27 positivity finding of 36% (22).

Although the majority of the patients escalated therapy to a TNFi because of physical examination findings of active disease, there were no differences regarding clinical disease status at 12 months post TNFi (active vs inactive vs remission). Furthermore, our study found that active enthesitis did not improve as dramatically as active arthritis did following 6 months of TNFi therapy. One consideration for this that the authors discussed was that because clinically identifying enthesitis in children is challenging, this may have impacted the overall enthesitis counts. This raises an important issue of whether we need more reliable physical examination techniques or imaging modalities for detecting enthesitis and sacroiliitis in this patient population. In a recent study, Weiss et al (23) assessed the accuracy of physical examination for the detection of sacroiliitis on MRI in patients with newly diagnosed JSpA and healthy controls. In this cohort, researchers found that the prevalence of reported inflammatory back pain symptoms and traditional physical examination measures used for detecting clinical sacroiliitis (eg, sacroiliac tenderness) were similar in those with MRI evidence of sacroiliitis and those without (23). Another study that compared the accuracy of ultrasound and clinical examination in patients with ERA found that ultrasound detected more active enthesitis counts compared with clinical examination (24). Better physical examination techniques or imaging modalities in this patient population would ultimately help guide the physician's decision on whether to escalate therapy to a TNFi. Patients with JSpA have also been shown to have higher pain scores compared with patients with other JIA subtypes (4). This concern led us to assess how much pain alone contributed to the decision to start a TNFi. However, pain without any accompanying definitive signs of active disease was not found to be a reason for escalation in our study.

In our study, TNFi therapy appeared to improve active joint and enthesitis counts and patient-reported pain at 6 months of TNFi therapy. This improvement in the active joint count was consistent with earlier studies that demonstrated the efficacy of TNFi for the treatment of arthritis in JSpA (12,13,25). Among 22 patients with ERA in the Dutch Arthritis and Biologicals in Children Register, the mean number of active joints decreased from 5.5 to 1 after 3 months of TNFi treatment (16). Hugle et al (12) showed in a study of 16 patients with JSpA treated with TNFi that 83% had achieved clinical remission 6 months into the treatment, although inferior efficacy was noted for control of sacroiliac joint disease. In our study, the active enthesitis count decreased, although this improvement was not as large as the decrease in the active joint count, especially for those starting on a TNFi for physical examination findings. Although the initial enthesitis count prior to TNFi initiation was less than the active joint count, it still did not completely resolve after 6 months of therapy. This may highlight the need for more effective therapy for enthesitis or, again, the need for better ways to measure enthesitis in children with JSpA. Additionally, the enthesitis count may be a prognostic indication and predictor of response to TNFi. In our study, we also found that the initial enthesitis count at the time patients started a TNFi was lowest in those who achieved clinical remission on medications at 12 months compared with those with active disease and inactive disease. Higher enthesitis counts may predict poorer response to TNFi therapy and poorer outcomes. However, there may be differences in disease phenotypes and disease progression that could account for some of the variations in response to TNFi, and this should be studied further.

Those patients with a shorter disease duration prior to starting a TNFi (<1 month after diagnosis) showed improvement in their arthritis only, but this was not as significant statistically or clinically as for those with a longer disease duration. Enthesitis did not improve at all in those who started on a TNFi with a disease duration of less than 1 month. Prior studies have shown that pediatric patients did not start a TNFi until 2 to 3 years after disease onset (10,15,16). In our study, the patients who initiated a TNFi very early in their disease course might have had more severe disease and potentially disease damage at the time of TNFi initiation.

In our study, we were limited to the data available from the medical record chart review. As previously mentioned, there was a large amount of missing data for certain JSpADA components,

which precluded us from using our initial outcome of interest, the total JSpADA scores, and assessing TNFi effect on axial disease (eg, presence of clinical sacroiliitis and abnormal back mobility). Analysis of the missing data suggested that data were not missing at random and were likely missing because of systematic processes with electronic medical record documentation that led to specific variables being repeatedly missing. We cannot exclude the possibility that potentially some of the variables that were not missing randomly might have contributed to the physician's decisions to escalate therapy. The missing variables also created a smaller patient population for some comparisons, which could introduce selection bias and threaten generalizability. We relied on a combination of ICD-9 codes to identify patients because there is not one specific ICD-9 code for the diagnosis of JSpA, and this might have also contributed to the smaller sample size and potential misclassification. Potential confounding by indication could explain some of the improvement seen in joint and enthesitis counts at 6 months post TNFi initiation. Patients who started a TNFi earlier might have had more severe disease, more active disease, other characteristics that would influence their overall outcome and response to TNFi therapy. Because TNFi are not traditionally first-line therapy, our cohort is likely to be considered high risk with active disease and thus needed to be exposed to a TNFi. Lastly, studies have shown that patients with JSpA report significant limitation in function from axial involvement (4); however, TNFi therapy's effect on axial disease in our study could not be assessed because of missing data on Schober's test for back mobility and Patrick's test for clinical sacroiliitis.

The reasons for which a physician escalates therapy in the JSpA population have not been formally evaluated before. Our hope is that by addressing the decision-making process and reasons why physicians escalate medication, we can ultimately improve outcomes. In our study, most physicians relied on their physical examination skills for detecting active disease to escalate therapy, and the group of patients who started a TNFi because of physical examination findings alone also had the largest improvement in their active joint counts. Our study also evaluated the effects of TNFi on arthritis and enthesitis. After 6 months of TNFi therapy, our patients had improvement in their peripheral symptoms. The effect on the active enthesitis count was not as great as that on the active joint count, which may highlight the need for better ways to measure and manage enthesitis. The management for JSpA has generally been adapted from that for adult ankylosing spondylitis or other JIA subtypes. Considering that more than half of our JSpA population continued to have active disease after 1 year of TNFi therapy, we need to consider whether this is the best approach and we need to find better ways to manage the pediatric JSpA population. Future studies should continue to look at the effect of TNFi and their role in the management of patients with JSpA, specifically those with predominantly enthesitis features.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Oliver had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Oliver, Simard, Lee, Sandborg.

Acquisition of data. Oliver, Simard, Lee.

Analysis and interpretation of data. Oliver, Simard, Lee, Gerstbacher, Sandborg.

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