Attainment of Inactive Disease Status Following Initiation of TNF-α Inhibitor Therapy for Juvenile Idiopathic Arthritis: Enthesitis-related Arthritis Predicts Persistent Active Disease

KATHERINE J. DONNITHORNE, RANDY Q. CRON, and TIMOTHY BEUKELMAN

ABSTRACT. ***Objective.*** To analyze the attainment of inactive disease following initiation of tumor necrosis factor-α (TNF-α) inhibitors in a heterogeneous cohort of children with juvenile idiopathic arthritis (JIA).
Methods. We performed retrospective chart review of all children with JIA at 1 academic center who had started TNF-α inhibitor therapy. We retrospectively determined inactive disease status according to the 2004 criteria of Wallace, *et al*. We evaluated inactive disease status at 1 year after initiation of TNF-α inhibitor and attainment of inactive disease at any point during the study period. Predictors of inactive disease were determined using univariate analyses and multivariable logistic regression models.
Results. A total of 125 patients started TNF-α inhibitors, and 88 patients had data available for the 1-year followup visit. Many patients (49%) started TNF-α inhibitors within 6 months of the diagnosis of JIA. Diverse JIA phenotypes were represented: at baseline, 29% of all patients had active enthesitis and only 23% had active polyarthritis. At the 1-year followup, 36 of 88 (41%) patients had inactive disease. Overall, 67 of 125 (54%) patients ever attained inactive disease status during the study period. In multivariable models, enthesitis-related arthritis (ERA) and higher Childhood Health Assessment Questionnaire (CHAQ) scores at baseline were independently associated with failure to later attain inactive disease status.
Conclusion. Treatment with TNF-α inhibitors appears to be less effective for attaining inactive disease status in patients with ERA or higher baseline CHAQ scores. Further studies are needed regarding the clinical effectiveness of TNF-α inhibitor therapy and the optimal treatment of ERA. (First Release Nov 15 2011; J Rheumatol 2011;38:2675–81; doi:10.3899/jrheum.110427)

Key Indexing Terms:
JUVENILE IDIOPATHIC ARTHRITIS   TUMOR NECROSIS FACTOR-α INHIBITOR
DISEASE STATUS   ENTHESITIS-RELATED ARTHRITIS

Tumor necrosis factor-α (TNF-α) inhibitors have been shown in randomized clinical trials to be efficacious for treatment of juvenile idiopathic arthritis (JIA) in children with active polyarthritis (i.e., 5 or more active joints)[1,2]. The clinical effectiveness of TNF-α inhibitors for treatment of JIA has been demonstrated in several cohorts[3,4,5]. However, uncertainty

K.J. Donnithorne, MD, University of Alabama School of Medicine; R.Q. Cron, MD, PhD, Professor of Pediatrics, Division of Pediatric Rheumatology; T. Beukelman, MD, MSCE, Assistant Professor of Pediatrics, Division of Pediatric Rheumatology, University of Alabama at Birmingham.

Address correspondence to Dr. T. Beukelman, The University of Alabama at Birmingham, 1600 – 7th Avenue South CPP 210, Birmingham, AL 35233-1711, USA. E-mail: tbeukelman@peds.uab.edu

remains regarding the optimal use of TNF-α inhibitors in clinical practice for children with JIA[6].

JIA is a heterogeneous condition that encompasses several disease phenotypes and that has been grouped into 7 categories by the most recent classification system[7]. However, the preponderance of published data regarding treatment with TNF-α inhibitors are derived from children with the JIA categories of rheumatoid factor (RF)-negative polyarthritis, RF-positive polyarthritis, and extended oligoarthritis[6]. Specifically, there are only sparse reports of the effectiveness of TNF-α inhibitors for treatment of patients with other categories of JIA [e.g., enthesitis-related arthritis (ERA), psoriatic arthritis (PsA), and persistent oligoarthritis], for patients with active arthritis in fewer than 5 joints irrespective of JIA category, and for patients with active enthesitis.

Not all patients who start therapy with TNF-α inhibitors will attain a state of inactive disease[8,9]; however, clinical predictors of attainment of inactive disease status have not been fully characterized. One important factor may be the elapsed time from the diagnosis of JIA to treatment with TNF-α inhibitors — the concept of a "therapeutic window" during

which disease outcomes may be significantly altered depending on initial therapies[10]. It has been shown that patients with JIA who spend less time in active disease states in the first 2 years following diagnosis are less likely to later develop an unremitting clinical course[11]. Some studies have demonstrated the benefit of early intensive therapy of JIA with TNF-α inhibitors[9,12] and additional studies of this question are currently under way. Less severe disease, as measured by lower active arthritis joint counts, has also been shown to be associated with a greater likelihood of attaining inactive disease status with TNF-α inhibitor treatment[9]. JIA phenotypes, such as the International League of Associations for Rheumatology category and the presence or absence of enthesitis, may also have predictive significance.

In September 2007, 2 of the authors established a new pediatric rheumatology center in a large population region where pediatric rheumatology services had not previously been available for more than 5 years. The absence of subspecialist pediatric rheumatology care resulted in a heterogeneous cohort of patients who were naive to TNF-α inhibitors; in general, only children with severe polyarthritis had started therapy with TNF-α inhibitors prior to the inception of the new pediatric rheumatology center. When the center was established, many children with prevalent active JIA but without severe polyarthritis were started on TNF-α inhibitors. Evaluation of the clinical responses of this cohort of children who had newly started TNF-α inhibitors allows for unique comparisons. This cohort, heterogeneous with regard to disease duration, JIA severity, JIA category, and prior treatment regimens, allowed a cross-sectional study of the effectiveness of TNF-α inhibitor therapy in clinical practice. The purpose of our study was to characterize the effectiveness of treatment with TNF-α inhibitors in all categories of JIA and to determine clinical predictors of inactive disease.

MATERIALS AND METHODS

Patients. Using electronic health records, we retrospectively identified all children at our center with JIA who had newly started treatment with a TNF-α inhibitor since September 1, 2007. In all cases, TNF-α inhibitors were initiated at the discretion of the treating pediatric rheumatologist. In general, TNF-α inhibitors were started for children with any active arthritis despite current therapy with methotrexate (MTX) and for children with 3 or more active joints at initial evaluation. Some children received TNF-α inhibitors for persistent enthesitis. We included patients who were previously naive to all TNF-α inhibitors and who had at least 1 followup visit after initiation. We excluded patients who started TNF-α inhibitors specifically for active uveitis in the absence of active arthritis or enthesitis. All data were collected through June 2010 using a standard form and were entered into a Microsoft Access database. Patients' JIA category[7] was determined using the JIA Calculator[13].

Institutional review board approval was obtained prior to study commencement.

Data collected. Basic demographic data were obtained, including age, sex, and date of JIA diagnosis. Reliable information about the date of first onset of arthritis symptoms was not available in the health record. The name of the TNF-α inhibitor and the initiation date and details of MTX and oral glucocorticoid use were noted. Previous MTX was defined as use for at least 1 month prior to the initiation of TNF-α inhibitor therapy. Concurrent MTX was defined as use of MTX simultaneously at any point during TNF-α inhibitor therapy. Chronic glucocorticoid was defined as daily oral prednisone or prednisolone use for at least 1 month immediately prior to the initiation of TNF-α inhibitor. A glucocorticoid burst was defined by a short oral course of prednisone or prednisolone (typically less than 1 month) that was initiated concurrently with the TNF-α inhibitor to provide immediate relief of the patient's symptoms.

Disease activity measures were recorded for each office visit, including number of joints with active arthritis (determined by the examining pediatric rheumatologist), presence or absence of active enthesitis (determined by the examining pediatric rheumatologist as localized tenderness of the patella at the 2-, 6-, or 10-o'clock position, at the insertion of the Achilles tendon on the calcaneus, and at the plantar fascia insertions on the calcaneus and on all metatarsal heads), physician global assessment of disease activity (0 to 100), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and Childhood Health Assessment Questionnaire (CHAQ) score. Patients were subsequently evaluated by the same pediatric rheumatologist as at the baseline visit at 92% of all followup office visits. ESR and CRP values were recorded with an office visit only if the values were obtained within 7 days of the visit. We retrospectively applied the 2004 inactive disease criteria of Wallace, *et al* to determine inactive disease status at each office visit[14]. These criteria require (1) no joints with active arthritis; (2) no fever, rash, serositis, splenomegaly, or generalized lymphadenopathy attributable to JIA; (3) no active uveitis; (4) normal ESR or CRP; and (5) that physician global assessment of disease activity indicates no disease activity. If neither ESR nor CRP values were obtained in association with an office visit, then this criterion for inactive disease was omitted, as reported by Ringold and colleagues[8]. If the number of joints with active arthritis or the physician global assessment of disease activity was not recorded, then the visit was excluded from the outcome analyses. The baseline visit was defined as the visit immediately prior to the first visit in which the patient was actively receiving a TNF-α inhibitor. The baseline visit was typically, but not necessarily, the visit during which the initial TNF-α inhibitor was first prescribed.

Study outcome. The primary outcome was the presence of inactive disease at 1 year after initiation of TNF-α inhibitor. We assigned the office visit that was closest to 12 months (± 3 months) after initiation of TNF-α inhibitor as the 1-year followup visit. We also identified patients who ever attained inactive disease status following initiation of TNF-α inhibitor. As a secondary outcome, we identified patients who attained clinical remission while taking medication, defined as 6 continuous months of inactive disease[14].

Statistical analysis. Comparisons between inactive disease status and JIA categories and baseline characteristics were made using chi-square, Fisher's exact, t test, and Wilcoxon rank-sum. Predictors of inactive disease at 1-year followup and at any time during the study were determined using logistic regression models. Clinical predictors included timing of initiation of TNF-α inhibitor, sex, JIA category, active polyarthritis at baseline visit, prior MTX, concurrent MTX, prior chronic glucocorticoid, glucocorticoid burst, and baseline clinical measures (ESR, CRP, active joint count, CHAQ, physician global assessment, presence of enthesitis). Significant predictors in univariate analyses (p < 0.10) were analyzed further using stepwise backward selection multiple variable regression models with removal of covariates at the level of p > 0.05. Statistical analyses were performed using Stata 10.0 (StataCorp, College Station, TX, USA).

RESULTS

During the study period, 125 patients started treatment with TNF-α inhibitors at our center and had at least 1 followup visit, making them eligible for our "ever inactive disease" analyses. The median duration of followup was 14.0 months (interquartile range 9.0 to 21.0 mo). The median number of followup visits during the entire study period was 4 (interquartile range 3 to 5 visits). Of these patients, 88 patients had 1-year followup visits available for analysis (3 patients

had 1-year followup visits that lacked physician global assessment of disease activity and were excluded). The characteristics of the study patients are shown in Table 1. The median duration from diagnosis to initiation of TNF-α inhibitor was about 6 months for all patients. Treatment with TNF-α inhibitors persisted once initiated: 84 patients (95%) were receiving TNF-α inhibitors at their 1-year followup visit. However, 11 patients (13%) had switched from the initial TNF-α inhibitor to a different one by the 1-year followup due to intolerance or inadequate response of the initial TNF-α inhibitor.

Diverse JIA phenotypes were represented in our cohort: only 23% of patients had the JIA categories typically reported in studies of TNF-α inhibitors (RF-negative and RF-positive polyarthritis and extended oligoarthritis). Patients with the ERA and PsA categories combined accounted for over one-half of the cohort. At their baseline visits, about one-third of all patients had active enthesitis and about three-quarters of patients did not have active polyarthritis. The presence of active enthesitis at baseline was not restricted to ERA and included 6 patients with PsA and 1 patient with undifferenti-

ated arthritis. No patients with systemic arthritis were started on TNF-α inhibitors during the study period.

Less than one-half of patients had prior MTX use. Nearly all patients (> 90%) received MTX concurrently with TNF-α inhibitor therapy. A small minority of patients were receiving chronic oral glucocorticoids when they started TNF-α inhibitors, but 40% started a glucocorticoid burst concurrently with the TNF-α inhibitor. Most patients (83%) began etanercept as the initial TNF-α inhibitor.

At the 1-year followup visit, 36 (41%) of 88 patients had inactive disease. Thirty-four patients did not have ESR or CRP testing performed at the 1-year followup visit. Of these patients, 21 (62%) met the other criteria for inactive disease, and 13 (38%) had active disease according to the physician global assessment. Three patients with physician global assessments of disease activity that indicated no disease activity had elevated ESR levels (ESR of 21, 22, and 42 mm/h). Among the 52 patients who did not have inactive disease at the 1-year followup visit, 26 had 1 or more joints with active arthritis, 9 had elevated ESR levels, and 44 had physician global assessments indicating active disease.

Table 1. Characteristics of the study patients.

Characteristic	All Patients, n = 125	Patients with 1-year followup, n = 88
Female (%)	75 (60)	54 (61)
Age at JIA diagnosis, yrs, median (IQR)	7.1 (3.7–11.8)	7.0 (3.4–11.8)
Months from diagnosis to initiation of TNF-α inhibitor, median (IQR)	6.6 (0.7–35.6)	5.6 (0–37.6)
Started TNF-α inhibitor within 6 mo of diagnosis (%)	61 (49)	45 (51)
JIA category (%)		
Persistent oligoarthritis	26 (21)	14 (16)
Extended oligoarthritis	6 (5)	4 (5)
RF-negative polyarthritis	17 (14)	14 (16)
RF-positive polyarthritis	5 (4)	3 (3)
Psoriatic arthritis	17 (14)	10 (11)
ERA	53 (42)	42 (48)
Undifferentiated	1 (1)	1 (1)
Methotrexate use (%)		
Prior	60 (48)	39 (44)
Concurrent	114 (91)	83 (94)
Oral glucocorticoid use (%)		
Prior chronic	14 (11)	8 (9)
Burst	50 (40)	40 (45)
Baseline clinical characteristics		
Joint count, median (IQR)	2 (1–4)	2 (1–4)
5 or more active joints at baseline (%)	28 (23)	20 (23)
Active enthesitis (%)	36 (29)	28 (32)
ESR, median (IQR)	11 (6–29)	12 (7–32)
CHAQ, median (IQR)	0.5 (0.12–1)	0.5 (0.12–1)
Physician global, median (IQR)	24 (18–35)	25 (18–38)
First TNF-α inhibitor (%)		
Etanercept	104 (83)	73 (83)
Infliximab	7 (6)	6 (7)
Adalimumab	14 (11)	9 (10)

IQR: interquartile range; JIA: juvenile idiopathic arthritis; TNF-α: tumor necrosis factor-α; RF: rheumatoid factor; ERA: enthesitis-related arthritis; ESR: erythrocyte sedimentation rate; CHAQ: Childhood Health Assessment Questionnaire.

Table 2 shows the JIA category-specific outcomes. In the RF-negative polyarthritis category (the category most widely studied with respect to TNF-α inhibitor treatment), 57% of patients had inactive disease at the 1-year followup. Patients with ERA were less likely to have inactive disease at the 1-year followup compared to patients with RF-negative polyarthritis (24% vs 57%, respectively; p = 0.02). By contrast, patients with persistent oligoarthritis and PsA had inactive disease at 1 year at similar proportions to those with RF-negative polyarthritis (64% and 60%, respectively). Overall, 67 (54%) of 125 patients ever attained inactive disease during the study period after starting TNF-α inhibitor therapy. Patients with ERA were less likely to have ever attained inactive disease status compared to those with RF-negative polyarthritis (43% vs 76%; p = 0.03).

Table 3 shows the proportion of patients found to have inactive disease according to notable baseline clinical characteristics. Patients with active enthesitis at baseline were less likely to have inactive disease at 1-year followup (p = 0.04) or at any time during the study period (p = 0.04). This result was not strictly due to persistent active enthesitis: 15 of 28 patients with baseline enthesitis did not have active enthesitis at 1-year followup and only 5 of the 21 patients with baseline enthesitis who did not attain inactive disease at 1-year followup had active enthesitis in the absence of concurrent active arthritis. Nine patients initiated TNF-α inhibitors for active enthesitis in the absence of active arthritis at baseline; 2 (29%) of 7 had inactive disease at 1-year followup and 4 (44%) of 9 had inactive disease at any time. Patients with CHAQ score < 1 at baseline were more likely to have inactive disease at 1-year followup (p = 0.01) and at any time during followup (p = 0.02) compared to patients with CHAQ score ≥ 1. Patients with normal ESR at baseline were less likely to attain inactive disease during the study period compared to patients with an elevated ESR at baseline (p = 0.07). There was no association between timing of the initiation of TNF-α inhibitors and inactive disease. This was true whether the category was defined at 2, 6, 12, or 24 months elapsed between diagnosis and initiation of TNF-α inhibitors or analyzed as an ordinal or continuous variable.

Table 3. Proportions of patients found to have inactive disease according to notable baseline clinical characteristics.

Characteristic	Inactive Disease at 1 Year (%)	Inactive Disease Ever (%)
Active enthesitis	7/28 (25)	14/36 (39)
No active enthesitis	29/60 (48)	53/89 (60)
p	0.04	0.04
CHAQ < 1	31/58 (53)	47/76 (62)
CHAQ ≥ 1	5/23 (22)	11/30 (37)
p	0.01	0.02
Normal ESR	13/40 (33)	26/58 (45)
Elevated ESR	10/23 (43)	19/29 (66)
p	0.4	0.07
Started TNF-α inhibitor ≤ 6 mo after diagnosis	18/45 (40)	35/61 (57)
Started TNF-α inhibitor > 6 mo after diagnosis	18/43 (42)	32/64 (50)
p	0.9	0.4

CHAQ: Childhood Health Assessment Questionnaire; ESR: erythrocyte sedimentation rate; TNF-α: tumor necrosis factor-α.

Table 4 shows the predictors of inactive disease. According to the multivariable regression models, the ERA category of JIA was a strong independent predictor of failing to attain inactive disease at 1 year or at any time during the study. A baseline CHAQ score < 1 was a comparably strong independent predictor of attaining inactive disease at the 1-year followup or at any time during the study. The number of followup visits per patient was included in the "inactive disease ever" regression model as a confounding factor but is not a clinically relevant predictor.

Twenty-two patients attained clinical remission on medication during the study period. This represents 18% of the total study population and 33% of the patients who ever attained inactive disease. Of note, 25 patients had inactive disease at their last study visit without ever attaining clinical remission on medication. A stepwise backward selection regression model that included the number of followup visits yielded results similar to the other study outcomes: ERA category (OR 0.13, 95% CI 0.03–0.63) and normal ESR at baseline (OR

Table 2. JIA category-specific outcomes.

JIA Category	Inactive Disease at 1 Year (%)	p*	Inactive Disease Ever (%)	p*
All	36/88 (41)		67/125 (54)	
Oligo persistent	9/14 (64)	0.7	16/26 (62)	0.3
Oligo extended	1/4 (25)	0.6	3/6 (50)	0.3
RF-negative polyarthritis	8/14 (57)	—	13/17 (76)	—
RF-positive polyarthritis	1/3 (33)	0.6	3/5 (60)	0.6
Psoriatic arthritis	6/10 (60)	1.0	8/17 (47)	0.2
ERA	10/42 (24)	0.02	23/53 (43)	0.03

* Comparison to RF-negative polyarthritis. JIA: juvenile idiopathic arthritis; Oligo: oligoarthritis; RF: rheumatoid factor; ERA: enthesitis-related arthritis.

Table 4. Predictors of inactive disease in patients after newly starting treatment with TNF-α inhibitor. OR < 1 signify decreased odds of attaining inactive disease.

Outcome	Predictors	Univariate OR (95% CI)	Multivariable Model OR (95% CI)
Inactive disease at 1-year followup	ERA (vs RF-negative poly)	0.23 (0.07, 0.84)	0.20 (0.07–0.56)
	Baseline CHAQ < 1	4.1 (1.4, 13)	5.7 (1.7–19)
	Active enthesitis	0.36 (0.13, 0.96)	—
Inactive disease ever	ERA (vs RF-negative poly)	0.24 (0.07, 0.82)	0.24 (0.08–0.75)
	Baseline CHAQ < 1	2.8 (1.2, 6.7)	6.0 (1.6–23)
	Normal ESR at baseline	0.43 (0.17, 1.1)	—
	Active enthesitis	0.43 (0.20, 0.95)	—
	No. followup visits	1.4 (1.1, 1.7)	1.5 (1.1–2.1)

TNF-α: tumor necrosis factor-α; RF: rheumatoid factor; ERA: enthesitis-related arthritis; ESR: erythrocyte sedimentation rate; CHAQ: Childhood Health Assessment Questionnaire.

0.25, 95% CI 0.06–0.99) predicted failure to attain clinical remission on medication.

Owing to the relatively large proportion of children with ERA in this cohort and the association of this JIA category with a decreased likelihood of attaining inactive disease, we performed repeat univariate analyses restricted to the 53 children with ERA. Initiation of TNF-α inhibitor within 2 months of diagnosis was negatively associated with attainment of inactive disease at 1 year (0% vs 34%; p = 0.02) and use of chronic prednisone at baseline was positively associated with attainment of inactive disease at 1 year (75% vs 18%; p = 0.04). Of note, children with and without active enthesitis at baseline were similarly likely to have active enthesitis at the 1-year followup (50% vs 40%, respectively; p = 0.5). Other than the number of followup visits (OR 1.5, 95% CI 1.0–2.1), no factors were associated with ever attaining inactive disease.

DISCUSSION

We analyzed the attainment of inactive disease status following the initiation of TNF-α inhibitors among a heterogeneous cohort of children with JIA at 1 academic center and observed that 41% had inactive disease at their 1-year followup visit. We also observed that patients with ERA and patients with higher baseline CHAQ scores were less likely to attain inactive disease. There was no association between the elapsed time from diagnosis to initiation of TNF-α inhibitor therapy and attainment of inactive disease status in our cohort.

Our findings of 54% inactive disease over the study period are comparable to the recent report from the German Etanercept Registry[9]. In that study, a large cohort of 787 patients with JIA were treated with etanercept and 48% of patients attained inactive disease during the study period. The patients in the German cohort had all received prior therapy with MTX or glucocorticoids and had been judged to have refractory disease; this may in part explain the slightly higher rate of inactive disease in our cohort, in which only about one-half of patients had received prior MTX. We observed a high rate of ever attaining inactive disease (76%) among patients in our cohort with RF-negative polyarthritis and a relatively low rate (43%) among patients with ERA.

There are limited reports of the effectiveness of TNF-α inhibitors for children with the ERA category of JIA. Early open-label case series reported significant clinical improvement in small numbers of children with ERA who started TNF-α inhibitors[15,16]. In the recent publication from the German Etanercept Registry, Papsdorf and Horneff reported that 60 (54%) of 112 children with ERA attained inactive disease following initiation of TNF-α inhibitor[9]. This result was comparable to the overall cohort of children with JIA (375 of 787; 48%). However, the presence or extent of enthesitis was not documented in the registry. The 2009 report from the Dutch etanercept registry contained only 5 patients with ERA out of a total of 146 children with JIA, and clinical outcomes for the patients with ERA were not reported separately[4].

The prevalence of enthesitis among children with JIA is not well described, but 10% of JIA patients in a recent large inception cohort were reported to have the ERA category[17] and enthesitis may occur in other categories of JIA as well[18]. Although enthesitis appears to affect more than 10% of children with JIA, appropriate management remains uncertain; in fact, the treatment of enthesitis was omitted from the 2011 American College of Rheumatology Recommendations for the Treatment of JIA owing to a lack of published studies[19]. In open-label case series of children with active enthesitis who started TNF-α inhibitors, Tse, *et al*[15] reported subsequent resolution of enthesitis in 9 of 9 patients, and Henrickson and Reiff[16] similarly reported resolution of enthesitis in 4 of 4 patients. Current clinical studies of enthesitis are challenging because enthesitis is not explicitly assessed by the pediatric core response variables commonly used in clinical trials[20] or the Wallace inactive disease criteria[14]; however, the presence of active enthesitis may be encompassed in the physician global assessment of disease activity, as is our practice. Clinical evaluation of enthesitis is subjective, and tender entheses may be found among otherwise healthy children without known JIA[21]; these facts present additional challenges to the study of enthesitis.

The association between lower baseline CHAQ scores and higher likelihood of attaining inactive disease status was not surprising, as higher CHAQ scores would be expected to be

associated with a longer and/or more severe course of JIA that may be less responsive to treatment with TNF-α inhibitors. The possible association between normal ESR and lower likelihood of attaining inactive disease was somewhat unexpected. This finding suggests that TNF-α inhibitors may be more effective in patients whose active disease is accompanied by robust active systemic inflammation as measured by elevation of serum inflammatory markers. Certain disease manifestations that are not necessarily accompanied by systemic inflammation, such as joint pain and enthesalgia, may respond less well to TNF-α inhibitors. However, patient-reported joint pain may increase the physician global assessment of disease activity and subsequently reduce the frequency of attainment of inactive disease. When Papsdorf and Horneff[9] explicitly included patient-reported pain as a criterion in a modified inactive disease measure, about 75% of patients with inactive disease according to the Wallace, et al[14] criteria were reclassified as having active disease. We did not collect patient- or parent-reported arthritis-specific pain measures in clinical practice and thus we cannot evaluate possible associations between subjective pain, response to treatment with TNF-α inhibitors, and attainment of inactive disease.

The use of combination therapy with MTX and TNF-α inhibitors for the treatment of JIA has been shown to be more effective than the use of TNF-α inhibitors alone in nonrandomized studies[9,22]. The differential effect of combination therapy could not be adequately evaluated in our cohort due to the > 90% prevalence of use and resultant very small comparator group who received TNF-α inhibitor alone. The high prevalence of combination therapy with MTX and TNF-α inhibitors may in part explain the higher proportion of patients attaining inactive disease status in this cohort. Similarly, we could not adequately evaluate the potential differential effect of individual TNF-α inhibitors on the attainment of inactive disease because most children started therapy with etanercept.

We identified difficulties in retrospectively applying the 2004 criteria of Wallace, et al[14] to health records generated in our routine clinical practice. Specifically, the requirement for normal inflammatory markers (ESR or CRP) was potentially limiting. The criteria do not stipulate when the inflammatory markers must be checked in reference to the corresponding clinical evaluation. We chose 7 days, although other time intervals may be preferred. Irrespective of the chosen time interval, many children will not have inflammatory marker studies performed near the time of every physician visit. A physician may choose not to obtain inflammatory markers if the results are unlikely to change clinical care — this may occur in at least 2 subsets of patients: those with prolonged quiescent disease and those with obvious active arthritis. We observed evidence for both these scenarios in our cohort. Excluding these patient evaluations from analyses would have resulted in a loss of over one-third of our sample. Instead, we followed the approach of Ringold and colleagues, who chose to ignore the inflammatory marker criterion when data were unavailable[8].

Our retrospective cohort study has limitations. Many patients with prevalent JIA and the most significant polyarthritis were treated with TNF-α inhibitors by other physicians prior to the inception of our pediatric rheumatology center. These patients were not included in our study because their initial clinical data are unavailable; however, all new initiators of TNF-α inhibitors since the inception of the center were included in our cohort, including some patients with incident significant polyarthritis. We did not find an association between the elapsed time from diagnosis of JIA to the initiation of TNF-α inhibitor and the subsequent attainment of inactive disease; however, data limitations did not allow us to similarly evaluate the elapsed time from first onset of arthritis symptoms to initiation of TNF-α inhibitor, which may have produced different results. Owing to the relatively short duration of followup and varied timing of office visits, we chose attainment of inactive disease as our primary outcome because it is a cross-sectional determination that is independent of previous or subsequent events. Clinical remission on medication reflects a more durable clinical response; analysis of this secondary outcome produced similar results. We were unable to reliably evaluate elapsed time from initiation of TNF-α inhibitor to attainment of inactive disease because of the varied timing of office visits. We did not collect precise measurements of enthesitis and relied upon the subjective physician assessment in the medical record. However, there is no widely established clinical assessment for enthesitis activity.

In this heterogeneous cohort of patients with JIA who started TNF-α inhibitor therapy, ERA category and higher CHAQ scores were associated with failure to later attain inactive disease status. Further studies are needed regarding the clinical effectiveness of TNF-α inhibitors for the treatment of JIA and the assessment and treatment of children with enthesitis-related arthritis.

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