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Attainment of Inactive Disease Status Following Initiation of TNF-α Inhibitor Therapy in a Heterogeneous Cohort of Children with Juvenile Idiopathic Arthritis: Enthesitis Related Arthritis Predicts Persistent Active Disease

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Abstract

Objective—To analyze the attainment of inactive disease following initiation of 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 one academic center who newly initiated 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 any point during the study period. Predictors of inactive disease were determined using univariate analyses and multivariable logistic regression models.

Results—125 patients initiated TNF -α inhibitors, and 88 patients had 1 year follow-up visit data available. Many patients (49%) initiated 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 1 year follow -up, 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 at 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.

INTRODUCTION

Tumor necrosis factor alpha (TNF-α) inhibitors have been shown in randomized clinical trials to be efficacious for the 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 the treatment of JIA has been subsequently demonstrated in several cohorts

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(3–5). However, uncertainty 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 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 the treatment of patients with other categories of JIA (e.g., enthesitis-related arthritis (ERA), psoriatic arthritis, and persistent oligoarthritis), for patients with active arthritis in less than 5 joints irrespective of JIA category, and for patients with active enthesitis.

Not all patients who initiate 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 underway. 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 ILAR category and the presence or absence of enthesitis, may also have predictive significance.

In September 2007, two 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 naïve to TNF-α inhibitors; in general, only children with severe polyarthritis had initiated 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 initiated on TNF-α inhibitors. Evaluation of the clinical responses of this cohort of children who newly initiated TNF-α inhibitors allows for unique comparisons. This heterogeneous cohort with regard to disease duration, J IA severity, JIA category, and prior treatment regimens allowed for a cross-sectional study of the effectiveness of TNF-α inhibitor therapy in clinical practice. The purpose of this study is to characterize the effectiveness of treatment with TNF -α inhibitors in all categories of JIA and to determine clinical predictors of inactive disease.

METHODS

Patients

Institutional Review Board approval was obtained prior to study commencement. Using electronic health records, we retrospectively identified all children at our center with JIA who newly initiated 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 initiated 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 naïve to all TNF-α inhibitors and who had at least one follow-

up visit after initiation. We excluded patients who initiated TNF-α inhibitors specifically for active uveitis in the absence of active arthritis or enthesitis. All data were collected up 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).

Data collected

Basic demographics 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. TNF-α inhibitor name and initiation date and details of MTX and oral glucocorticoid use we re 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 treatment. A glucocorticoid burst was defined by a short oral prednisone or prednisolone course (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(as 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 positions, 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 the baseline visit at92% of all follow-up office visits. The 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.) 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 has been previously reported by Ringold, Wallace, 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 the 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 follow-up 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 on 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 tests. Predictors of inactive disease at 1 year follow -up 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 further analyzed using step-wise 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 initiated treatment with TNF -α inhibitors at our center and had at least one follow-up visit, making them eligible for our “ever inactive disease” analyses. The median duration of follow-up was 14.0 months with an interquartile range of 9.0 to 21.0 months. The median number of follow-up visits during the entire study period was4 with an interquartile range of 3 to 5 visits. Of these patients, 88 patients had 1 year follow -up visits available for analysis(3 patients had 1 year follow-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 approximately 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 follow -up visit. However, 11 patients (13%) had switched from the initial TNF-α inhibitor to a different one by the 1 year follow-up 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 positive polyarthritis and extended oligoarthritis). Patients with the ERA and psoriatic arthritis categories combined accounted for over one-half of the cohort. At their baseline visits, approximately one-third of all patients had active enthesitis and approximately 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 psoriatic arthritis and 1 patient with undifferentiated arthritis. No patients with systemic arthritis were initiated on TNF-α inhibitors during the study period.

Less than one-half of patients had prior MTX use. Nearly all patients (>90%) received methotrexate concurrently with TNF-α inhibitor therapy. A small minority of patients were receiving chronic oral glucocorticoids when they initiated 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 follow-up visit, 36 of 88 (41%) patients had inactive disease. Thirty-four patients did not have ESR or CRP testing performed at the one year follow -up 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 levels of 21, 22, and 42 mm/hour). Among the 52 patients who did not have inactive disease at the 1 year follow-up 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 2 shows the JIA category-specific outcomes. In the RF negative polyarthritis category (the most widely studied category with respect to TNF-α inhibitor treatment) 57% of patients had inactive disease at the one year follow-up. Patients with ERA were less likely to

have inactive disease at the 1 year follow-up compared to patients with RF negative polyarthritis (24% vs. 57%; p = 0.02). By contrast, patients with persistent oligoarthritis and psoriatic arthritis had inactive disease at 1 year at similar proportions to RF negative polyarthritis (64% and 60%, respectively). Overall, 67 of 125 (54%) patients ever attained inactive disease during the study period after initiating TNF-α inhibitor therapy. Patients with ERA were less likely to have ever attained inactive disease status compared to 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 follow-up (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 follow-up and only 5 of the 21 patients with baseline enthesitis who did not attain inactive disease at 1 year follow-up 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 of 7 (29%) had inactive disease at 1 year follow-up and 4 of 9 (44%) had inactive disease at any time. Patients with CHAQ score < 1 at baseline were more likely to have inactive disease at 1 year follow -up (p = 0.01)and at any time during follow -up (p = 0.02)compared to patients with CHAQ score ≥ 1. Patients with a 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 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. Ab aseline CHAQ score less than 1 was a comparably strong independent predictor of attaining inactive disease at the 1 year follow-up or at any time during the study. The number of follow-up 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 step -wise backward selection regression modelth at included the number of follow -up visits yielded similar results to the other study outcomes: ERA category (OR 0.13 (0.03 – 0.63)) and normal ESR at baseline (OR 0.25 (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 follow-up (50% versus 40%; p = 0.5). Other than the number of follow-up visits(odds ratio 1.5 (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 one academic center and observed that 41% had inactive disease at their 1 year follow-up 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 this study, a large cohort of 787 JIA patients 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 methotrexate or glucocorticoids and had been determined to have refractory disease; this may in part explain the slightly higher rate of inactive disease in our cohort in which only approximately one-half of patients had received prior methotrexate. 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 initiated TNF -α inhibitors (15, 16). In the recent publication from the German Etanercept Registry, Papsdorf and Horneff reported that 60 of 112 (54%) of 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). Despite the fact that enthesitis appears to affect more than 10% of children with JIA, its appropriate management remains uncertain; infact, 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 initiated TNF-α inhibitors, Tse, *et al* reported subsequent resolution of enthesitis in 9 of 9 patients (15)and Henrickson, *et al* similarly reported resolution of enthesitis in 4 of 4 patients (16). Current clinical studies of enthesitis are challenging because enthesitisis not explicitly assessed by the pediatric co re 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. The 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 explicitly included patient -reported pain as a criterion in a modified inactive disease measure, approximately 75% of patients with inactive disease according to the Wallace *et al* criteria were re -classified as having active disease (9). We did not collect patient or parent reported arthritis-specific pain measures in clinical practice and thus 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 methotrexate 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 non-randomized studies (9, 22). The differential effect of combination therapy could not be adequately evaluated in our cohort due to the greater than 90% prevalence of use and resultant very small comparator group who received TNF-α inhibitor alone. The high prevalence of combination therapy with methotrexate 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 initiated 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, though 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 of 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 prior approach of Ringold, Wallace, and colleagues, who chose to ignore the inflammatory marker criterion when data were unavailable (8).

This 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 this 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 follow-up 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 prior 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 owing to the varied timing of office visits. We did not capture precise measurements of enthesitis and relied upon the subjective physician assessment contained in the medical record. However, there is no widely established clinical assessment for enthesitis activity.

In conclusion, in this heterogeneous cohort of patients with JIA who initiated 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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Table 1

Characteristics of the study patients.

Characteristic	All Patients (N = 125)	Patients with 1 year follow-up (N =88)
Female	75 (60%)	54 (61%)
Age in years at JIA diagnosis		
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)
Initiated TNF-α inhibitor within6 months of diagnosis	61 (49%)	45 (51%)
JIA category		
Persistent oligoarthritis	26 (21%)	14 (16%)
Extended oligoarthritis	6 (5%)	4 (5%)
RF-polyarthritis	17 (14%)	14 (16%)
RF+ polyarthritis	5 (4%)	3 (3%)
Psoriatic	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)
MD 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 alpha; RF, rheumatoid factor; ERA, enthesitis-related arthritis; ESR, erythrocyte sedimentation rate; CHAQ, Childhood Health Assessment Questionnaire)

Table 2

JIA category-specific outcomes

JIA Category	Inactive Disease at 1 year	p value*	Inactive Disease ever	p value*
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-polyarthritis	8/14 (57%)	---	13/17 (76%)	---
RF+ polyarthritis	1/3 (33%)	0.6	3/5 (60%)	0.6
Psoriatic	6/10 (60%)	1.0	8/17 (47%)	0.2
ERA	10/42 (24%)	0.02	23/53 (43%)	0.03

(JIA, juvenile idiopathic arthritis; Oligo, oligoarthritis; RF, rheumatoid factor; ERA, enthesitis-related arthritis)

* p value for comparison to RF-polyarthritis.

Table 3

Proportions of patients found to have in active disease according to notable baseline clinical characteristics.

Baseline 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 value	0.04	0.04
CHAQ < 1	31/58 (53%)	47/76 (62%)
CHAQ ≥ 1	5/23 (22%)	11/30 (37%)
p value	0.01	0.02
Normal ESR	13/40 (33%)	26/58 (45%)
Elevated ESR	10/23 (43%)	19/29 (66%)
p value	0.4	0.07
Initiate TNF-α inhibitor ≤ 6 months after diagnosis	18/45 (40%)	35/61 (57%)
Initiate TNF-α inhibitor > 6 months after diagnosis	18/43 (42%)	32/64 (50%)
p value	0.9	0.4

(CHAQ, Childhood Health Assessment Questionnaire; TNF-α, tumor necrosis factor alpha)

Table 4

Predictors of inactive disease after newly initiating treatment with TNF-α inhibitor. Odds ratios less than 1 signify decreased odds of attaining inactive disease.

Outcome	Predictors	Univariate Odds Ratio	Multivariable model Odds Ratio
Inactive disease at 1 year follow-up	ERA (vs RF-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-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)	------
	Number of follow-up visits	1.4 (1.1 – 1.7)	1.5 (1.1 – 2.1)

(TNF-α, tumor necrosis factor alpha; RF, rheumatoid factor; ERA, enthesitis-related arthritis; ESR, erythrocyte sedimentation rate; CHAQ, Childhood Health Assessment Questionnaire)