Changes in Body Mass Index in Children with Juvenile Idiopathic Arthritis Treated with Tumor Necrosis Factor Inhibitors

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ABSTRACT. ***Objective.*** To evaluate changes in body mass index (BMI) among cohorts of children with juvenile idiopathic arthritis (JIA) with and without tumor necrosis factor (TNF) inhibitor therapy.

Methods. We performed a retrospective chart review of children with JIA who newly initiated TNF inhibitor therapy and had at least 1 year of subsequent followup (TNF cohort). We also included children with JIA and at least 1 year of followup without any TNF inhibitor therapy (comparator cohort). Children with systemic arthritis were excluded. Age and sex specific BMI z-scores and their corresponding categories (normal, overweight, obese) were determined. We compared changes from a baseline visit to the last followup visit using t-test for BMI z-scores and chi square and Kruskal-Wallis tests for BMI categories.

Results. The TNF cohort had 167 patients; the comparator cohort had 37. The median study followup was 2.8 and 2.2 years, respectively. The cohorts had similar age, sex, race, weight, and height distributions. The TNF cohort had a statistically significant increase in BMI z-score from baseline (+0.15; $p = 0.02$) that was not significantly different from the increase (+0.09) observed in the comparator cohort ($p = 0.5$). There was no significant change in the proportions of overweight and obese children in the TNF cohort compared to baseline ($p = 0.6$) or compared to the change in the comparator cohort ($p = 0.2$).

Conclusion. Over more than 2 years of followup, we did not observe a significant increase in BMI among children with JIA receiving TNF inhibitor compared to those not receiving it. (J Rheumatol First Release Dec 1 2013; doi:10.3899/jrheum.130159)

Key Indexing Terms:
JUVENILE IDIOPATHIC ARTHRITIS BODY MASS INDEX
TUMOR NECROSIS FACTOR INHIBITOR

Juvenile idiopathic arthritis (JIA) is the most common rheumatic disease in children and may result in significant short-term and longterm morbidity[1]. Fortunately, the advent of highly effective biologic therapeutic agents, such as the tumor necrosis factor (TNF) inhibitors, has dramatically improved outcomes for children with JIA. TNF inhibitors are now considered one of the main therapies for the treatment of JIA[2]. However, inhibition of TNF may lead to excessive weight gain[3,4,5,6,7,8,9], a particularly worrisome possibility in light of the current epidemic of childhood obesity[10]. This excessive weight gain in childhood may persist into adulthood[11,12], irrespective of future treatment.

The term "rheumatoid cachexia" has been coined to refer to the body habitus of patients with rheumatoid arthritis (RA) and is attributed to high levels of TNF-α, a cytokine also known as cachexin[3]. TNF-α is associated with increased resting energy expenditure, decreased fat-free mass, and decreased appetite[4]. Thus, there is reason to suspect that the use of TNF inhibitors could directly alter a patient's body mass and composition, perhaps leading to excessive weight gain[3,4,5]. Clinical studies of adults with various inflammatory conditions, such as rheumatoid arthritis, spondyloarthropathy, and plaque psoriasis, have yielded mounting evidence that confirms an association between TNF inhibitor therapy and weight gain[6,7,8,9].

The association between TNF inhibitor therapy and weight gain is less thoroughly studied among children with JIA. Therefore, we retrospectively evaluated changes in BMI among cohorts of children with JIA in the presence and absence of TNF inhibitor therapy.

MATERIALS AND METHODS

Patients. Using electronic medical records, we retrospectively identified all children with JIA treated at the Division of Pediatric Rheumatology at the

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University of Alabama at Birmingham/Children's of Alabama since its inception in September 2007. All therapeutic decisions, including the use of TNF inhibitors, were determined by the treating pediatric rheumatologist as part of usual care. In general, TNF inhibitors were initiated for children with any active arthritis despite more than 2 months of therapy with methotrexate (MTX) or for children with 3 or more joints with active arthritis at the time of any clinical evaluation, irrespective of current or prior therapy[13].

We retrospectively categorized children with JIA into 2 cohorts: TNF inhibitor users and a comparator cohort of children without TNF inhibitor use. Children who satisfied the following inclusion criteria were eligible for the TNF inhibitor cohort: (1) at least 1 clinic visit with BMI measurement prior to the first initiation of TNF inhibitor therapy; and (2) at least 1 clinic visit with BMI measurement following a minimum of 365 days of uninterrupted therapy after first initiation of TNF inhibitor. Children who had a minimum of 365 days of clinical followup with BMI measurements prior to any use of TNF inhibitor were eligible for the comparator cohort. The following exclusion criteria were applied to the TNF inhibitor and comparator cohorts: (1) systemic arthritis [no children with systemic arthritis received TNF inhibitor at our center and most children received systemic glucocorticoids (GC), known to frequently cause excessive weight gain]; and (2) biopsy diagnosis of inflammatory bowel disease. Children could have potentially contributed observations to the comparator cohort and then the TNF inhibitor user cohort sequentially, but no children in this study met both sets of inclusion criteria. Owing to difficulty in interpreting and categorizing BMI scores in children younger than 2 years old[14], children in the comparator cohort could not begin followup before reaching 2 years of age and children who initiated TNF inhibitor therapy before 2 years of age were excluded.

Data collected. All data were collected through May 2012 using a standardized Microsoft Access database form. Institutional review board approval was obtained prior to beginning the study. Basic demographic data were obtained, including sex, self-reported race, date of birth, date of JIA diagnosis, and category of JIA. Height in centimeters and weight in kilograms were measured at each clinic visit by appropriately trained medical staff and using the same stadiometer and scale. Medication use was determined from the physician note and active medication lists. Any use of systemic GC and MTX during the study period was noted. Whether the treating physician believed a patient currently had clinically inactive disease (not necessarily according to the preliminary criteria of Wallace[15]) was also recorded at each visit in a standardized fashion.

BMI was calculated in kg/m^2 for each clinic visit. BMI values were transformed into age and sex specific z-scores (SD scores) according to US Centers for Disease Control and Prevention data from 2000, because the distribution of normal BMI scores varies with age[14,16]. BMI measurements were also categorized as normal, overweight, or obese according to established age-specific and sex-specific cutpoints[17].

The baseline visit in the TNF inhibitor cohort was defined as the most recent visit immediately prior to the first visit in which the patient was actively receiving TNF inhibitor therapy. This was most commonly the visit at which TNF inhibitor therapy was first prescribed. The baseline visit in the comparator cohort was defined as the first visit after attaining the age of 2 years.

The last followup visit in the TNF inhibitor cohort was defined as the most recent visit at which the patient was actively receiving TNF inhibitor therapy. Interruptions in TNF therapy (owing to inactive disease) following the initial 365 days of uninterrupted therapy were permitted. The last followup visit in the comparator cohort was defined as the most recent visit prior to the initiation of TNF inhibitor, if any.

Outcome. The primary study outcome was the change in BMI z-score between the baseline visit and the last followup visit. A secondary outcome was the change in BMI category (normal, overweight, and obese) over the same time period. We also evaluated the change in BMI z-score between the baseline visit and the visit closest to 12 months later, provided that this visit was between 9 and 15 months after the baseline visit.

Statistical analysis. Comparisons between basic demographic features were made using chi-square for categorical variables and Wilcoxon rank-sum for continuous variables. Comparisons of BMI z-scores were made using t test. Comparisons of BMI categories between the cohorts at the baseline and the last followup visits were made using chi-square. The comparison of the change in BMI categories between the cohorts was made by assigning a point value to each BMI category (normal = 1, overweight = 2, obese = 3) and using the Kruskal-Wallis test. Statistical analyses were performed using STATA 10.0 (StataCorp).

RESULTS

Retrospective review of electronic medical records identified 167 patients who met criteria for the TNF inhibitor cohort and 37 patients who met criteria for the comparator cohort. Many patients with JIA had an insufficient duration of followup for inclusion in either cohort. Table 1 shows the demographic characteristics of both cohorts. In both the TNF and comparator cohorts, the majority of patients were female and white. The median age at diagnosis of JIA and the median age, weight, and height at the baseline visit were similar in both cohorts. The categories of JIA differed significantly between the cohorts ($p < 0.001$), with the majority of children in the comparator cohort having persistent oligoarthritis and the most frequent JIA categories in the TNF inhibitor cohort being enthesitis-related arthritis and rheumatoid factor–negative polyarthritis. A much greater proportion of patients in the TNF inhibitor cohort received treatment with MTX and with any systemic GC ($p < 0.001$ for both comparisons) compared to the comparator cohort. Patients treated with TNF inhibitor had longer study followup time than those in the comparator cohort ($p = 0.004$), but both cohorts had a median of over 2 years of study followup. All patients in the TNF inhibitor cohort were receiving TNF inhibitor at their last followup study visit, and 78% had uninterrupted TNF inhibitor therapy throughout the entire study period. No patients had received a biologic agent of a different therapeutic class prior to receiving TNF inhibitor.

Table 2 shows the BMI and BMI z-scores from the baseline visit and the last followup visit for both cohorts. The mean BMI and BMI z-score increased numerically in both cohorts during the study period. The increase in BMI z-score in the TNF inhibitor cohort was statistically significant ($p = 0.02$), but the increase in the comparator cohort was not ($p = 0.5$). The increase in BMI z-scores from baseline visit to last followup visit between the 2 cohorts was not significantly different ($p = 0.7$). Similarly, the change in BMI z-scores was not different 12 months after the baseline visit, with a mean BMI z-score increase of 0.08 in both cohorts ($p = 1.0$).

Figure 1 shows the distribution of change in BMI z-score for each of the 2 cohorts. The data suggest that there is no significant difference between the TNF inhibitor and comparator cohorts, even among those with extreme changes in BMI z-score.

Table 3 shows the distribution of patients' BMI

Table 1. Characteristics of the study patients.

Characteristics	Patients Receiving TNF Inhibitors, n = 167	Patients Not Receiving TNF Inhibitors, n = 37	p
Race, n (%)			
White	146 (87)	32 (86)	0.2
African American	18 (11)	4 (11)	
Hispanic	0	1 (3)	
Other	1 (0.6)	0	
Unknown	2 (1)	0	
Female, n (%)	104 (62)	24 (65)	0.8
JIA category, n (%)			< 0.001
Oligo persistent	26 (16)	20 (54)	
Oligo extended	8 (5)	1 (3)	
RF– polyarthritis	39 (23)	5 (14)	
RF+ polyarthritis	6 (4)	0	
Psoriatic	26 (16)	5 (14)	
ERA	56 (34)	6 (16)	
Undifferentiated	6 (4)	0	
Age at JIA diagnosis, yrs, median (IQR)	7.9 (4.0–12.7)	9.1 (5.0–12.8)	0.8
Age at baseline visit, yrs, median (IQR)	10.2 (6.6–14.2)	10.3 (6.4–13.5)	0.8
Weight at baseline visit, kg, median (IQR)	37 (22–55)	39 (22–49)	0.5
Height at baseline visit, cm, median (IQR)	140 (119–162)	136 (114–153)	0.4
BMI z-score, mean (SD)	0.49 (1.21)	0.25 (1.16)	0.3
Followup time, yrs, median (IQR)	2.8 (2.2–3.5)	2.2 (1.4–3.0)	0.004
Systemic GC use	120 (72)	10 (27)	< 0.001
MTX use	159 (95)	22 (59)	< 0.001

TNF: tumor necrosis factor; JIA: juvenile idiopathic arthritis; oligo: oligoarthritis; RF: rheumatoid factor; ERA: enthesitis-related arthritis; IQR: interquartile range; BMI: body mass index; GC: glucocorticoids; MTX: methotrexate.

categories (normal, overweight, obese) at the baseline visit and the last followup visit for each cohort. There was no difference in the proportion of patients in each BMI category in each of the 2 cohorts at the baseline visit ($p = 0.6$) or the last followup ($p = 0.2$). Although the mean BMI z-score increased in the comparator cohort, there was no change in the distribution of BMI categories (3 patients increased 1 BMI category and 3 patients decreased 1 BMI category). There was an increase in the proportion of patients in the overweight and obese BMI category in the TNF inhibitor cohort; 2 patients increased 2 BMI categories, and 23 patients increased 1 BMI category. (Conversely, 1 patient decreased 2 BMI categories and 8 patients decreased 1 BMI category.) Nevertheless, these differences in the BMI category distributions between the baseline and last followup visit among children in the TNF inhibitor cohort were not significant ($p = 0.4$). Additionally, there was no difference in the change in BMI category between the 2 cohorts ($p = 0.2$).

Among children in the TNF inhibitor cohort, 123 of 167 patients (74%) achieved a state of clinically inactive disease (according to treating physician opinion) at any visit during the study period. There was no difference in the change in BMI z-scores between those children who achieved inactive disease at least once (+0.18) and those who did not (+0.04; $p = 0.3$).

DISCUSSION

We retrospectively analyzed changes in BMI z-scores among children with JIA initiating treatment with TNF inhibitor and a comparator cohort of children with JIA who did not receive TNF inhibitor. We observed a small but statistically significant increase in the BMI z-score over a median of 2.8 years after initiation of TNF inhibitor therapy, but this increase was not significantly different from that observed in the comparator cohort. To our knowledge, this is the first study to investigate the association between TNF inhibitor treatment and BMI among children with JIA using a cohort approach, as opposed to a cross-sectional study. Of note, 1 published single-center cross-sectional study of 154 children with JIA did not find an association between current TNF inhibitor use and obesity or overweight[18].

Many studies have demonstrated a positive association between TNF inhibitor and weight gain among adults with inflammatory diseases. In a 2-year randomized study of 40 adults with early RA who failed treatment with MTX, the addition of treatment with TNF inhibitor was associated with an increase in body fat mass compared to the addition of sulfasalazine and hydroxychloroquine (mean increase of 3.8 kg vs 0.4 kg; $p = 0.04$), independent of disease activity[6]. Similarly, in a retrospective cohort of 53 adults with RA, there was a significant increase in mean weight of 1.9 kg ($p = 0.02$) between 1 year prior to initiating treatment with

Table 2. BMI at baseline visit and last followup visit for patients treated with TNF inhibitors and those not treated with TNF inhibitors.

	Baseline Visit		Last Followup Visit		Mean Change		p Value for Change in BMI	
	Mean BMI	Mean BMI z-score	Mean BMI	Mean BMI z-score	BMI	BMI z-score	Within Cohort	Between Cohorts
Patients Receiving TNF Inhibitors, n = 167	20.1	0.49	21.9	0.63	+1.8	+0.15	0.02	0.7
Patients Not Receiving TNF Inhibitors, n = 37	19.1	0.25	20.2	0.34	+1.1	+0.09	0.5	

BMI: body mass index in kg/m^2; TNF inhibitor: tumor necrosis factor inhibitor.

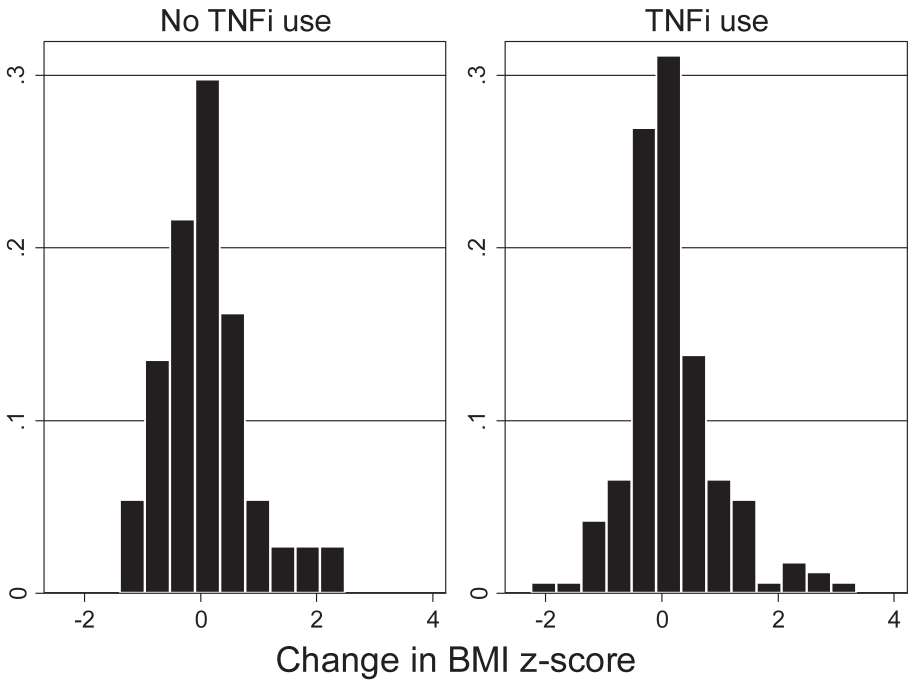

Figure 1. Histogram of the change in body mass index (BMI) z-score between the baseline visit and last followup visit among children treated with tumor necrosis factor (TNF) inhibitors and those not treated with TNF inhibitors.

Table 3. Patients' BMI categories at baseline visit and last followup visit, by TNF inhibitor use. Data are n (%).

	Baseline Visit				Last Followup Visit			
	Normal	Overweight	Obese	p	Normal	Overweight	Obese	p
Patients Receiving TNF Inhibitor	115 (69)	28 (17)	24 (14)	0.6	104 (62)	33 (20)	30 (18)	0.2
Patients Not Receiving TNF Inhibitor	28 (76)	6 (16)	3 (8)		28 (76)	6 (16)	3 (8)	

BMI: body mass index; TNF: tumor necrosis factor.

TNF inhibitor and 1 year after the start of treatment[7]. A prospective 2-year study of 106 adults with spondyloarthropathy who initiated TNF inhibitor therapy found a mean increase in fat mass of 1.5 kg ($p < 0.001$)[8]. Significant increases in BMI were also observed in 98 adults with plaque psoriasis 6 months after initiation of TNF inhibitor therapy that were not observed in 43 comparator patients treated with MTX, and 24 patients (24%) treated with TNF inhibitor gained between 4 and 10 kg during the study[9].

Although it appears likely that TNF inhibitor use results

in weight gain among many adult patients with inflammatory diseases, the results of our study suggest that this may not be the case among most children with JIA. The potential explanations for this discrepancy are unclear, but may relate to ongoing growth, greater daily physical activity, the pathogenesis of JIA, or differences in the role of TNF-α in determining body composition in children.

Although we did not observe an increase in BMI z-scores that was different between the children treated with TNF inhibitor and those who were not, it is unclear what constitutes a clinically relevant increase in BMI z-scores. Several studies have investigated the minimum decrease in BMI z-scores among obese children that is clinically relevant. Some studies show that a decrease of at least 0.25 z-score units is necessary for clinical benefit[19,20], although other studies have shown that smaller changes can be clinically relevant[21]. At the population level, increasing BMI z-scores may be linearly related to complications of overweight, even within the healthy range[22], but to our knowledge, there have not been published studies about the minimum increase in BMI z-scores that correlates with diminished health among individual children.

Our study had important limitations. Height and weight measurements were obtained by appropriately trained medical staff members as part of routine care, but a strict protocol for obtaining these measurements was not undertaken. Our sample size was modest, especially for the comparator cohort, but was similar to other published studies and likely did not obscure any clinically significant changes in BMI at the population level. One reason for our relatively small comparator group is that about 75% of all children with JIA at our center receive treatment with biologic agents, primarily TNF inhibitor. This proportion is considerably higher than the 45% recently reported from the Childhood Arthritis and Rheumatology Research Alliance (CARRA) Registry[23]. It is unclear how this treatment practice may have affected the results of our study. Our comparator cohort also had important differences from the TNF inhibitor cohort, for example there was less systemic GC use. However, because we did not observe differences in BMI z-scores between the 2 cohorts, we did not analyze for the possibility of confounding factors. We cannot exclude the possibility that a small minority of children with JIA experience idiosyncratic weight gain with TNF inhibitor therapy; this should be considered further. From our available data, we could not know the precise day that the first dose of TNF inhibitor was received at home. We used the BMI measurements from the most recent visit immediately prior to the first visit in which the patient was actively receiving TNF inhibitor therapy. Both the mean and median duration of time between these visits was 3 months and the BMI z-score was not significantly different between these visits ($p = 0.08$). Therefore, it is unlikely that significant weight loss or gain occurred between the baseline BMI measurement and the actual initiation of TNF inhibitor. Nevertheless, if significant weight gain occurred during this time (caused by systemic GC therapy, for example), it would have been attributed to TNF inhibitor under our study assumptions, and we did not observe a significant increase in BMI z-score following TNF inhibitor initiation. Because there have been reports of excessive weight gain in adults associated with both etanercept and monoclonal antibody TNF inhibitor (i.e., infliximab), we grouped all TNF inhibitor use together in our study. When users of etanercept and monoclonal antibody TNF inhibitor were analyzed separately and compared to each other, there were no significant differences in BMI z-score changes ($p = 0.4$). BMI is not the only available measure for the assessment of weight gain in children, but its use has been widely adopted[16], and a recent study of children with rheumatic diseases demonstrated significant increases in BMI z-score associated with treatment with systemic GC[24]. Increases in patients' weights may have been attributable to increases in lean mass and therefore increases in BMI z-scores may not always have reflected undesired weight gain. We did not include data from children without JIA, but the proportions of overweight and obese children in our study appear comparable to those from the general population[25].

Our study of children with JIA did not demonstrate significant weight gain associated with the use of TNF inhibitor therapy. It does not appear that concern for excessive weight gain should generally limit the use of TNF inhibitor in the treatment of a typical child with JIA.

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