

# High Doses of Infliximab in the Management of Juvenile Idiopathic Arthritis

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**ABSTRACT. Objective.** To review our experiences with high-dose infliximab (IFX) to treat juvenile idiopathic arthritis (JIA). We routinely use high doses of IFX (10–20 mg/kg) in children with recalcitrant or highly active JIA. Although biologics have revolutionized treatment of JIA, many patients have active disease despite therapy. Studies have shown benefits of high-dose IFX in several conditions, including inflammatory bowel disease, psoriasis, and idiopathic uveitis. The safety and effectiveness of high-dose IFX have not been evaluated in JIA.

**Methods.** We performed a retrospective review of children with JIA who received IFX  $\geq$  10 mg/kg. We recorded all serious adverse events (SAE), medically important infections, and infusion reactions. We also recorded the physician global assessment of disease activity (MD global) and active joint count (AJC) at initiation of high-dose IFX and 3, 6, and 12 months thereafter.

**Results.** Fifty-eight subjects received a total of 1064 infusions over 95 person-years. There were a total of 9 SAE (9.5/100 person-yr), 7 of which were potentially related to therapy, and 6 infusion reactions (0.5%), none constituting anaphylaxis. Statistically significant improvements were observed in the AJC (median 0, range 0–31, vs 2, 0–39) and MD global (12, 2–31, vs 22, 5–80) over the first year.

**Conclusion.** High-dose IFX appears safe in the management of JIA. Future prospective controlled studies are necessary to evaluate its safety and efficacy. (First Release Aug 15 2013; J Rheumatol 2013;40:1749–55; doi:10.3899/jrheum.130133)

## Key Indexing Terms:

JUVENILE IDIOPATHIC ARTHRITIS

INFLIXIMAB

THERAPEUTICS

Juvenile idiopathic arthritis (JIA) can result in longterm morbidity, including chronic pain and physical disability lasting into adulthood<sup>1,2,3</sup>. Use of biologics, such as tumor necrosis factor (TNF) inhibitors, has resulted in substantial short-term and longterm improvements in patient outcomes<sup>5</sup>, and is also of substantial benefit in pediatric ulcerative colitis and Crohn disease<sup>6</sup>. Two anti-TNF agents, etanercept and adalimumab, have been approved by the US Food and Drug Administration (FDA) for treatment of children with JIA<sup>4</sup>, while infliximab (IFX) is widely perceived as being effective but does not have an FDA-approved indication in JIA<sup>5,7,8</sup>. IFX is approved for use in Crohn disease, rheumatoid arthritis (RA), ankylosing spondylitis, psoriasis, psoriatic arthritis, and ulcerative colitis<sup>9</sup>, with approved starting doses of 3–5 mg/kg every 6–8 weeks depending on the indication. However, studies of children with uveitis and adults with inflammatory bowel

disease (IBD) have shown that dose intensification can lead to improved responses<sup>10,11,12,13</sup>. Indeed, doses as high as 10–20 mg/kg have been reported to be effective in the management of childhood uveitis<sup>10,14</sup>, and the FDA label for RA permits doses as high as 10 mg/kg every 4 weeks. The safety of these higher doses remains largely unknown, however.

The general safety of anti-TNF agents such as IFX has long been a matter of concern<sup>15</sup>. An early metaanalysis of randomized trials demonstrated an increased risk of infections and malignancies among patients with RA taking IFX compared to placebo-treated patients, with the malignancy risk being dose-dependent<sup>16</sup>. In 2009, the FDA released a report of 48 children who developed malignancies while under treatment with anti-TNF agents<sup>17</sup>, a report that has been criticized on methodological grounds<sup>18,19</sup>. More recently, pharmacoepidemiologic studies using medical claims data have failed to detect a higher risk of serious bacterial infections or malignancies among patients with JIA treated with anti-TNF agents compared to those taking nonbiologic disease-modifying antirheumatic drugs (DMARD) or those not taking any immunosuppressant therapy<sup>20,21</sup>.

Based upon empirical evidence, it is our clinical practice to use high doses of IFX (at least 10 mg/kg/dose) in many of our patients with JIA, particularly those who are refractory

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Accepted for publication May 24, 2013.

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to other anti-TNF agents or to standard doses of IFX, have highly active arthritis, or have organ-threatening complications such as uveitis. The safety and efficacy of this approach has not previously been reported. Consequently, this study was undertaken to evaluate retrospectively the number and types of selected adverse events that occurred in a cohort of patients with JIA who received at least 1 dose of 10 mg/kg of body weight of IFX at a single academic medical center. As a secondary analysis, we also evaluated changes in active joint count (AJC) and physician global assessment of disease activity (MD global) after starting high-dose IFX.

MATERIALS AND METHODS

*Patients.* This was a retrospective study of children with JIA evaluated by 1 or more pediatric rheumatologists at Children’s of Alabama (COA) who received at least 1 high dose of IFX (≥ 10 mg/kg) at any time between January 1, 2006, and June 30, 2012. Patients were identified in the electronic health record using *International Classification of Diseases*, 9th edition, codes for JIA and medication records for treatment with IFX. The study was limited to children meeting the International League of Associations for Rheumatology criteria for JIA<sup>22,23</sup>.

Our study was in compliance with the Declaration of Helsinki. Institutional Review Board approval at the University of Alabama at Birmingham was obtained.

*Data collection.* Data were collected for all visits through June 2012 using a standardized form and entered into a Microsoft Access database. Patients are typically evaluated every 3–4 months, when measures of active arthritis (e.g., AJC, MD global assessment of disease activity) are documented into a standard computerized data entry form. Basic demographic data, indices of disease activity, medication use, weight, IFX dosage, and safety events were recorded at all visits for each patient. Ninety percent of infusions took place at COA, so we likely have nearly complete data on infusion reactions, whether major or minor. In contrast, safety events that took place at home may not always have been reported; however, any hospitalizations at COA were documented, and it is highly likely that hospitalizations and other significant illnesses that occurred elsewhere would have been documented in a telephone note or subsequent visit. Thus, aside from infusion reactions, we report only serious adverse events (SAE) and medically important infections.

*Outcomes.* The primary safety outcomes were the following: (1) all SAE according to the FDA definition (any events resulting in death, hospitalization or prolongation of existing hospitalization, significant loss of function, or congenital anomaly); (2) all medically important infections (requiring intravenous antimicrobial therapy or hospitalization); (3) all infusion reactions; and (4) all events resulting in temporary or permanent discontinuation of therapy. With the exception of infusion reactions, we included safety events that occurred up to 3 months after the most recent dose of IFX. The likelihood of causation for each event was assessed and agreed upon by 2 reviewers (MLS, TB).

We also evaluated clinical effectiveness, including the MD global (range 0–100) and the AJC at the initiation of high-dose IFX and at 3, 6, and 12 months. In this retrospective study, we did not have reliable access to most of the other items in the core set<sup>24</sup>. As we did not have standardized outcome variables for patients with uveitis, we limited the effectiveness analysis to subjects in whom the indication for high-dose IFX was active arthritis.

*Statistical analysis.* Continuous data were reported as medians and ranges, and categorical data were reported as percentages. Comparisons of efficacy data at baseline versus 3, 6, and 12 months posttherapy were performed with the paired Mann-Whitney U test. Analyses were performed using

PASW-Version 17. To adjust for multiple comparisons, a p value < 0.01 was considered statistically significant.

RESULTS

*Subjects.* Fifty-eight subjects were included in our study; their demographic and clinical backgrounds are shown in Table 1. High-dose IFX was used in 48 patients because of active arthritis or enthesitis and in 10 patients because of uveitis. In general, patients with uveitis underwent intensification as a result of either active uveitis or the inability to taper topical corticosteroids. Twenty-two (38%) of the subjects had previously received standard doses of IFX (Table 2), and 49 (84%) had received either another TNF inhibitor or standard doses of IFX prior to receiving high-dose IFX. Fifty-seven (98%) of the patients were taking concomitant nonbiologic DMARD therapy, usually weekly subcutaneous methotrexate (MTX). Fifty-five (95%) of the patients received IFX infusions at intervals ranging from 2–4 weeks, although the infusions were spaced to every 6–8 weeks in 9 of those patients, reflecting our practice of decreasing the frequency of infusions in patients with prolonged periods of disease inactivity. Thirty-eight (66%) of 58 patients continued IFX until the end of the study period; of the other 20, 2 discontinued because of adverse events, 8 for lack of effectiveness, 3 owing to quiescent disease, 1 because of financial cost, and 1 as a result of difficulties with intravenous access. Five were lost to followup. One additional patient who discontinued therapy because of adverse events reinstituted it after 10 months. Thus, including a 3-month window after the most recent infusion in all but the 5 patients who were lost to followup, there were a total of 1046 infusions over 95

Table 1. Patient population. Continuous data are shown as median (minimum-maximum).

Characteristic	N (%)	Uveitis*, n (%)
n	58	10 (17)
Male:female	26:32 (45% male)	3:7 (30% male)
Race/ethnicity		
Hispanic or Latino	1 (1.7)	1 (10)
White	51 (88)	8 (80)
African American	6 (10)	1 (10)
JIA subtype		
Persistent oJIA	6 (10)	4 (67)
Extended oJIA	3 (5.2)	1 (33)
RF– polyarticular	21 (36)	1 (4.8)
RF+ polyarticular	0	0
Psoriatic	9 (16)	2 (22)
ERA	19 (33)	2 (11)
Systemic JIA	0	0
Age at diagnosis, yrs	8.9 (1.5–15.8)	4.8 (1.5–11.7)
Age high-dose infliximab started, yrs	11.9 (2.2–18.4)	7.8 (2.2–12)

\* Subjects for whom indication for high-dose infliximab was uveitis. ERA: enthesitis-related arthritis; JIA: juvenile idiopathic arthritis; oJIA: oligoarticular JIA; RF: rheumatoid factor.



Table 2. Infliximab usage. Continuous data are shown as median (range).

Characteristic	N (%)
Indication	
Active arthritis	48 (83)
Uveitis associated with JIA	10 (17)
Maximum dose, mg/kg	15.5 (10–23.8)
Duration of therapy, months	13.3 (1.6–55)
No. infusions per patient	14 (3–84)
Highest frequency of infusions	
Every 2–3 weeks	18 (31)
Every 4–5 weeks	37 (64)
Every 6–8 weeks	3 (5.2)
Concurrent therapy	
Methotrexate	55 (95)
Other DMARD	8 (14)
Any DMARD	57 (98)
Oral prednisone	8 (14)
Prior biologic therapy	
Etanercept	34 (59)
Adalimumab	13 (22)
Standard doses of infliximab	22 (38)
Abatacept	3 (5.2)
Anakinra	0
Any biologic, including prior infliximab	49 (84)
Discontinuation of therapy	20 (34)
Adverse events	2 (3.4)
Lack of effectiveness	8 (14)
Disease quiescence	3 (5.2)
Financial cost	1 (1.7)
Lost to followup	5 (8.6)
Difficult intravenous access	1 (1.7)

Concurrent therapies were defined as those taken at onset of infliximab course. DMARD: disease-modifying antirheumatic drug; JIA: juvenile idiopathic arthritis.

person-years of exposure to high-dose IFX available to examine.

**Safety.** A summary of safety events is shown in Table 3. A total of 9 SAE were experienced by 8 patients during therapy, for a rate of 9.5/100 person-years. Of those, 7 were possibly or probably related to the medicine, with the remainder judged unlikely to be related. The events potentially related to IFX therapy included acute psychiatric events in 2 patients without documented psychiatric histories prior to initiation of TNF inhibitor therapy; infected dental hardware in 1 patient (secondary to melanotic tumor of infancy, which preceded use of IFX); idiopathic cervical lymphadenopathy in 1 patient; hospitalization for fever, neutropenia, and elevated liver function tests in 1 patient; hospitalization for diabetic ketoacidosis in 1 patient; and hospitalization for pyelonephritis in another. The child with the lymphadenopathy underwent biopsy of the lymph node, which was found to be negative for malignancy or infection. For the patient with fever and neutropenia, no etiology of these events was found, and the symptoms and laboratory abnormalities resolved over a few days. Of the 2 events not thought to be related to the

medicine, an obese child was hospitalized for a liver biopsy on account of elevated liver function tests and found to have nonalcoholic steatohepatitis attributed to obesity, and another child was hospitalized with an asthma attack.

No other medically important infections occurred in any of the patients; thus, with the pyelonephritis and the infected dental hardware the only 2 documented infectious adverse events during the treatment period, the rate of medically important infections was 2.1/100 person-years. Of those, 1 patient was receiving 20.3 mg/kg/dose and the other 11.6 mg/kg/dose; neither was taking concomitant corticosteroids. There were no malignancies or deaths. Six infusion reactions were reported by 5 patients (0.5% of infusions). None of them constituted anaphylaxis; in all of the infusion reactions, the children were stable upon discharge from the infusion center. Two of the infusion reactions took place an unspecified number of hours to 1 day after the infusion; 1 constituted shortness of breath (with normal chest radiograph) and the other palpitations. The relationship of both events to IFX therapy is unclear. Three patients discontinued therapy because of adverse events, including 2 following potential infusion reactions and 1 following a hospital admission for psychiatric events. Of those 3, one restarted without event and continued the therapy at the end of the data collection period.

**Effectiveness.** We compared the MD global assessment of disease activity and AJC at the onset of IFX therapy versus at 3, 6, and 12 months, limiting the analysis to patients in whom the indication for IFX was active arthritis (Table 4). We performed paired tests, comparing each patient to his or her baseline value. Statistically significant improvements were observed in the AJC and MD global at all timepoints. Similar results were observed when the population was limited to subjects who had previously received standard doses of IFX, although because of limited numbers of subjects, the differences are of borderline statistical significance (Table 5).

As an illustration of the requirement for high-dose IFX, one of the subjects in this report is a Hispanic female diagnosed at age 4 years with extended oligoarticular JIA, treated with IFX on account of uveitis. Prior therapies included MTX and adalimumab, followed by standard doses of IFX. At age 7 years, her IFX dose was increased to 20 mg/kg, which she received every 2 weeks. Repeated attempts to space the infusions to every 3 weeks resulted in objective flares of her uveitis, which was controlled again at the 2-week intervals.

**Comparison to standard doses of IFX.** Twenty-six subjects received standard doses of IFX (5–9 mg/kg/dose), including 22 who were subsequently switched to high doses; the other 4 remained on standard doses throughout the data collection period. Including a 3-month window for safety monitoring, the total duration of therapy was 24.2 patient-years, during which time they received 203 infusions. During this therapy,



**Table 3.** Safety of high-dose infliximab. Serious adverse events were included regardless of perceived association with infliximab therapy. Reported infusion reactions occurring within 24 h of administration were also included.

Type	n	Resulted in Discontinuation	Relationship with Infliximab Therapy
Serious adverse events			
Severe psychiatric events	2	1 of 2	Possible
Admitted for liver biopsy	1	No	Unrelated
Asthma attack	1	No	Unrelated
Fever and neutropenia	1	No	Possible
Diabetic ketoacidosis	1	No	Possible
Infected dental hardware	1	No	Probable
Cervical lymphadenopathy	1	No	Possible
Pyelonephritis	1	No	Possible
Infusion reactions			
Flushing, tachycardia	1	No	Definite
Shortness of breath	1	No	Unlikely (hours after infusion)
Chest pain	1	Yes	Definite
Red streak on arm	1	Yes	Possible; pt restarted without event 10 months later
Palpitations	1	No	Unlikely (day after infusion)
Flushing and nausea	1	No	Definite

**Table 4.** Effectiveness of high-dose infliximab.

	n	MD Global Median (range)	p*	n	Active Joint Count Median (range)	p*
Baseline	43	20 (5–80)	NA	45	2 (0–34)	NA
3 months	31	10 (2–35)	< 0.001	31	1 (0–20)	0.002
6 months	22	10 (2–35)	0.001	22	0 (0–6)	0.001
12 months	27	12 (2–31)	0.001	27	0 (0–31)	0.001

\* p values are pairwise comparisons to patients with data at the indicated timepoint compared to baseline. Because of the exclusion of patients in whom the indication for infliximab therapy was uveitis, the number of subjects depicted in this table is lower than the total number of subjects in the study. MD global: physician global assessment of disease activity; NA: not applicable.

**Table 5.** Effectiveness of high-dose infliximab among patients previously treated with standard doses (5 to < 10 mg/kg) of infliximab.

	n	MD Global Median (range)	p*	n	Active Joint Count Median (range)	p*
Baseline	15	20 (5–80)	NA	15	2 (0–34)	NA
3 months	10	10 (2–35)	0.021	10	0 (0–12)	0.007
6 months	7	10 (2–34)	0.201	7	0 (0–2)	0.093
12 months	10	11 (2–31)	0.05	10	0 (0–31)	0.027

\* p values are pairwise comparisons to patients with data at the indicated timepoint compared to baseline. Because of the exclusion of patients in whom the indication for infliximab therapy was uveitis, the number of subjects depicted in this table is lower than the total number of subjects in the study who had previously received standard doses of infliximab. MD global: physician global assessment of disease activity; NA: not applicable.

2 SAE occurred, both attributable to underlying psychiatric conditions. Thus, the incidence of SAE among patients taking standard doses of IFX was 8.3/100 person-years. Additionally, 2 infusion reactions occurred, of which 1

constituted possible anaphylaxis, although the symptoms resolved without therapy. Thus, the rate of infusion reactions was 1.09% of infusions, which was similar to that observed under high-dose IFX (0.5%).



## DISCUSSION

We report on 58 children with JIA who received doses of IFX of at least 10 mg/kg/dose (range 10–24 mg/kg/dose). Our results primarily demonstrate the safety of this approach. During 95 person-years of high-dose IFX exposure, only 7 SAE occurred that were possibly or probably related to therapy, out of a total of 9 SAE. Although the incidence of SAE was slightly lower among patients taking standard doses of IFX (8.3/100 person-yrs) compared to high-dose (9.5/100 person-yrs), the incidence of SAE was similar to that reported by Ruperto and colleagues in their longterm extension study of a randomized trial of standard-dose IFX in children with JIA: 17 SAE among 78 patients during 171 person-years of followup (9.9/100 person-yrs)<sup>7</sup>.

Additionally, we observed an incidence of medically important infections of 2.1/100 person-years. This rate is also similar to that reported from the longterm extension study of IFX, in which 3 medically important infections (2 cases of pneumonia and 1 reactivation of tuberculosis, all of which were classified as SAE), occurred during 171 person-years of followup, for a rate of 1.8/100 person-years<sup>7</sup>. Our observed rate of medically important infections was also similar to those observed in a prospective clinical registry of 397 patients with JIA treated with the anti-TNF agent etanercept (1.78/100 person-yrs with concomitant MTX and 2.05/100 person-yrs without MTX<sup>25</sup>) and in a study that used medical claims to identify hospitalized infections among 1315 children with JIA treated with any anti-TNF agent (3.5/100 person-yrs)<sup>20</sup>.

Lastly, we reported infusion reactions in 6/1046 infusions (0.5%), compared to 5.6% in the Ruperto study<sup>7</sup>. None of the infusion reactions we observed under high-dose IFX therapy constituted anaphylaxis. Previous studies have shown that the risk of infusion reactions is lower with moderate doses of IFX (e.g., 5–10 mg/kg) compared to low doses (3 mg/kg)<sup>26,27</sup>, so it is plausible that even higher doses (10–20 mg/kg) may reduce the risk even further. The mechanism by which higher doses may reduce immunogenicity is unclear; it may relate to continuing tolerance induction, which would not occur if trough levels dropped to zero<sup>28</sup>. Additionally, it is well established that concomitant DMARD therapy is protective against the development of human antichimeric antibodies<sup>26,27</sup>; this was employed in 57 of 58 patients. Overall, therefore, the safety profile of high-dose IFX in conjunction with weekly MTX compared favorably to typical doses of IFX and other anti-TNF agents reported previously.

Multiple studies have shown dose responsiveness to IFX in patients with RA, psoriasis, and IBD<sup>11,28,29,30,31</sup>. Trachana, *et al* reported that increasing the adalimumab dose to weekly was of benefit in some children with JIA<sup>32</sup>, although this has not been reported in RA. A metaanalysis demonstrated a dose-response curve for all biologics in the

treatment of RA<sup>33</sup>. Thus, our experience and that of others<sup>10,11,14,32</sup> suggests that the ideal dose may vary according to the disease and age of the patient, plus unknown and unpredictable individual factors possibly including the intensity of inflammation, both systemic and localized in the joint<sup>34</sup>.

Our study has several limitations. Because of its retrospective design, there was no prospective standardized collection of safety event data. Nevertheless, it is unlikely that we overlooked many SAE, because our patients and referring physicians typically contact us when a child is being admitted to the hospital, particularly when the admission may relate to the patient's underlying disorder or its therapy. Further, we systematically reviewed every office visit, infusion note, and telephone note in our electronic medical record to ensure that we recorded as many SAE as possible, and as noted, 90% of the infusions took place at COA. A second limitation is that because this was not a controlled study, we were unable to compare effectiveness of high doses of IFX to standard doses. We can only report that in general, children improved with high-dose IFX, including children who had previously been treated with standard doses. Additionally, because this was not an intention-to-treat trial, discontinuations due to ineffectiveness could potentially have skewed the analysis, although the median duration of therapy among the 8 who discontinued for that reason was 13 months (longer than our period of analysis), and all of them had at least 3 months of data (data not shown). Effectiveness analysis is further complicated by use of IFX to treat enthesitis, which is not identified in the AJC; in this retrospective study, it would be challenging to distinguish when the switch was made owing to enthesitis versus arthritis, or both. To the extent that the change was made as a result of enthesitis alone, this would bias our findings toward the null hypothesis (no effectiveness) insofar as AJC is concerned, although improvements in enthesitis would likely be identified by the MD global. A final limitation is the absence of standardized outcome data on uveitis, which were not readily available in the medical record.

To our knowledge, this is the first report of the use of high-dose IFX to treat arthritis in children with JIA, and it is one of the largest reports on the use of IFX doses exceeding 10 mg/kg/dose. We have not identified any new short-term safety concerns in our cohort, which had a median of 13 months of followup, with a maximum of almost 5 years. Although 20 patients (34%) were not receiving therapy at the end of the followup period, 5 of those were lost to followup; only 2 discontinued because of SAE. This does not rule out the possibility of increased risk of infections (especially in regions of the world endemic for tuberculosis<sup>35</sup>), but overall our results are reassuring. Additionally, with acknowledgment of the limitations of assessing effectiveness through chart review, our study does appear to



show that high-dose IFX may be of benefit for AJC and the MD global, even among patients previously treated with standard doses. Future work should include a prospective analysis of the safety and effectiveness of standard versus high-dose IFX therapy in children at high risk of complications of JIA.

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