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Safety and Efficacy of High-dose Tumor Necrosis Factor (TNF) Inhibitors in the Management of Pediatric Inflammatory Diseases

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Abstract

Objectives: To review a cohort of patients receiving higher than standard or FDA approved dosing of TNF inhibitors to assess the safety and efficacy of these agents in the management of inflammatory joint and eye disease in a clinical pediatric rheumatology setting.

Methods: A retrospective review was performed of patients 1-17 years of age with inflammatory diseases requiring TNF inhibitor therapy treated with at least six weeks of treatment of a higher than the standard FDA approved dose of TNF inhibitors, from 12/1/11-4/8/14. Entanercept (Enbrel) was given at doses greater than 0.8 mg/kg, Infliximab (Remicade) was infused in doses greater than 5 mg/kg or more frequently than every eight weeks, and Adalimumab (Humira) was given at either 20 mg/kg weekly for patients weighing less than 30 kg or 40 mg/kg weekly for patients weighing greater than 30 kg. Serious adverse events (SAE), infections, and infusion reactions were all documented. We also noted clinical improvement based on parent/patient's report of decreased symptoms and provider assessment, including exam findings and laboratory parameters.

Results: Thirty-five patients were included (average 11.3 years). Of these, 24 (68%) were noted to have improvement of either symptoms or exam. There was one SAE noted in the group and one infusion reaction, and 10 patients with illnesses that may have been exacerbated by immune suppression.

Conclusion: Higher than standard-dose or FDA approved dosing of TNF inhibitors appear safe and efficacious in the management of pediatric inflammatory diseases, however, caution must be taken with interpretation of the results due to the retrospective chart review study design. Larger, prospective, controlled studies will be necessary to more fully evaluate safety and efficacy of this treatment approach.

Keywords: Tumor necrosis factor inhibitors; Entanercept; Infliximab; Adalimumab; Pediatric inflammatory diseases; Biologic therapy safety

Introduction

Pediatric inflammatory diseases include a wide spectrum of clinical pathology, including juvenile idiopathic arthritis (JIA) [1]. Treatment of these diseases has only relatively recently included the use of biologic response modifiers, in particular Tumor Necrosis Factor (TNF) inhibitors [2]. Previous studies have shown the safety and efficacy of biologics in the treatment of pediatric inflammatory diseases [3-6]. Recent studies have also shown that higher dose treatment can lead to improved responses in children with some refractory diseases [6-8]. However, the safety of immune suppressive therapy, such as biologics, is an area of continued interest, particularly as pertains to risk of infections and possible malignancies [9].

In our clinical practice we frequently treat patients with refractory disease or serious onset disease with higher than FDA-approved doses of Etanercept (ET; greater than 0.8 mg/kg/dose, weekly), Infliximab (IFX; greater than 5 mg/kg/dose or more frequently than every eight weeks), or Adalimumab (AD; 20 mg/kg/week for patients less than 30 kg and 40 mg/kg/week for patients greater than 30 kg every two weeks). In regard to the safety of biologics, there have been increasing data on long-term outcomes, with reassuring findings reported in several studies [5,10-13]. However, the safety and efficacy of higher dose biologics for pediatric patients with a diversity of diseases have not been reported. We therefore conducted this review primarily to assess safety in a cohort of patients in our academic medical center with pediatric inflammatory disease who received at least six weeks of higher dose anti-TNF therapy. As a secondary analysis, we also attempted to assess clinical improvement based on patient report of symptoms, provider physical exam, and laboratory assessment.

Materials and Methods

Patients

We performed a retrospective study of children with inflammatory diseases evaluated at Helen DeVos Children's Hospital (HDVCH) who received higher than FDA-approved doses of either ET (greater than 0.8 mg/kg/dose), IFX (greater than 5 mg/kg/dose or more frequently than every 8 weeks), or AD (20 mg/kg/week for patients less than 30 kg and 40 mg/kg/week for patients greater than 30 kg) for at least a 6

week period between December 1, 2011 and April 8, 2014. Except in selected instances, such as the two uveitis patients with vision threatening disease, the majority of patients were started on standard dose therapy. The other exceptions included a patient with JIA and two with juvenile spondyloarthritis that had previously been on higher dose etanercept prior to changing agents. The other patients were dose escalated only after standard follow up had failed to show adequate or complete response. Our standard follow up interval is 3 months. Dose escalation is typically attempted after 1-2 follow up intervals, and usually in patients who are partial responders but with early tapering of drug effect. Patients were identified using the electronic medical record for treatment with ET, IFX, or AD. The study was limited to children receiving higher than FDA-approved doses for duration of at least six weeks. This study was approved by the hospital Institutional Review Board.

Data collection

Data were collected on all patient encounters until April 8, 2014 and entered into a Microsoft Excel (Redmond, WA, USA) spreadsheet. Patients were typically evaluated every 3-4 months in the clinic, but more frequently if they required IFX infusions (every 28 days to 8 weeks depending on the patient). Basic demographic data, indices of disease activity, concurrent medication use, weight, TNF inhibitor type and dosage, and safety events were all recorded.

Statistical analysis

Patient outcomes including adverse reactions, response to therapy, and continuation of therapy were summarized. Continuous data are reported as medians and ranges, and categorical data are reported as percentages.

Results

Subjects

Thirty-five patients were included in the review. Demographic and clinical background data are shown in Table 1. High-dose TNF inhibitors were used in this patient population for refractory disease unresponsive to standard doses.

Characteristics	**N(%)**
Gender	
Male:Female	11:24(31%:69%)
Race/ethnicity	
Caucasian	30(85%)
Hispanic	3(8%)
Mixed/Other	2(5%)
Diagnoses	
JIA	27(77%)
Uveitis	2(5%)
Ankylosing spondylitis	1(2%)
Spondyloarthritis	1(2%)
Blau's Syndrome	1(2%)
Erythrodermic psoriasis	1(2%)
ANA+recurrent fever	1(2%)
Psoriatic arthritis	1(2%)
Age high-dose biologic started (y)[a]	11.3(1-17)
JIA: Juvenile Idiopathic Arthritis; ANA+: Positive For Antinuclear Antibodies; [a]Data expressed as the median (range)	

Table 1: Patient characteristics.

Five patients (14%) started on a high-dose TNF inhibitor without first starting on a standard dose, as described above in the methods section, 14(40%) had received a different biologic before being treated with high dose therapy, while the majority, 16 (45%) had received the same biologic agent at standard prior to being placed on a higher dose (Table 2). Twenty-two (62%) of the patients were taking concomitant methotrexate, while 25(71%) were on a concomitant NSAID. Five patients (14%) were on concomitant sulfasalazine. Patients were on a high dose biologic for a median of 41 weeks, with a range of 10 weeks to 103 weeks. Twenty-four (80%) patients continued on the high dose biologic through the review period.

Concurrent therapy	**N(%)**
Methotrexate	22(62)
Meloxicam	15
Naproxen	5
Diclofenac	5
Sulfasalazine	5(14)
Prednisone	6
Methylprednisolone	1
Celecoxib	2
Mercaptopurine	1
Azathioprine	1
Prior biologic therapy[a]	
Adalimumab	7
Entanercept	4
Adalimumab and Entanercept	1
Abatacept	1
Canakinumab	1
Started on high dose	5
[a]Other than same biologic at standard dose	

Table 2: Therapy.

Safety

A summary of events is shown in Table 3. Only one serious safety event was experienced by our patient population. This patient experienced peripheral neuropathy while on infliximab, which resolved with discontinuing the medication. Four (11%) infusion reactions while on infliximab were documented. One patient reported a sensation of "throat closing". The latter patient was seen in the emergency department and discharged. One patient with tachypnea and urticaria was admitted to the hospital from the infusion center for observation and also discharged soon after. Neither event led to any sequelae. The other two patients' symptoms were very mild and did not require further intervention other than slowing infusion rate. Each of these four patients continued on infliximab after the described events and tolerated the high dose with future infusions with by slowing the infusion rates or by adjusting premedication. Of the infections listed, seven were considered minor illnesses. Two skin abscesses were noted, one was treated with an outpatient incision and drainage by their primary care doctor without complication. The other was also noted to have healed without complication, although details of treatment were not available.

Type of event	N	TNF-inhibitor	Resulted in discontinuation
Serious adverse event			
Peripheral neuropathy	1	IFX	Yes
Infusion reaction			
Urticaria	1	IFX	No
Urticaria with tachypnea	1	IFX	No
Flushing with bradycardia	1	IFX	No
Throat swelling	1	IFX	No
Infections			
Skin abscess formation	2	IFX	No
Minor infections			
Sinus	1	ETN, IFX	No
Upper respiratory	5	ETN, ADA, IFX	No
Acute otitis media	1	ADA	No
IFX: Infliximab; ETN: Etanercept; ADA: Adalimumab			

Table 3: Safety of high-dose TNF inhibitors.

Effectiveness

The patient's progress was assessed by review of physical exam findings, laboratory studies, imaging, and physician and patient global assessment. Of our 35 patients, 24 (68%) had evidence of clinical improvement (Table 4).

Outcome	N(%)
Improved	24(68)
Not improved	9(25)
Discontinued because of side effects	1(2)
Lost to follow-up	1(2)

Table 4: Effectiveness of high-dose TNF inhibitors.

Discussion

Our findings demonstrated that a higher than standard or FDA approved dose of entanercept, infliximab, or adalimumab may be used in the treatment of pediatric patients with inflammatory diseases without any significant increase of serious safety events. With a median of 41 weeks of exposure to a high-dose biologic, there was only one SAE. However, neuropathy is reported in standard doses of TNF inhibitor therapy as well [14-16] and cannot be attributed to high dose administration. In our patient, these symptoms resolved after cessation of therapy. In addition, we only observed nine minor infectious illnesses during the treatment period. None of these illnesses required hospitalization, and only two required specific intervention, namely incision and drainage. Finally, we observed four infusion reactions. All four patients were continued on high-dose therapy without further reactions. As with any retrospective case review, this study has several limitations, the most important is the lack of an active control group. There is, however, ample data from original studies and long term outcome studies to enable a historical comparison to the efficacy of high doses of biologics to standard doses or those on traditional DMARDs alone. None of the adverse events we report are inconsistent with the findings noted in prior published experience with these agents, and the nearly 70% response rate is convergent with prior reports as well [17-21]. Notably, Lovell et al. demonstrated rates of SAEs to be 0.13 per patient-year, and rates of serious infections were 0.04 per patient-year, in a total etanercept exposure of 225 patient-years. Of their 32 patients with complete efficacy data who received etanercept for greater than or equal to four years, 94% achieved an ACR Pediatric 30 response and 78% achieved an ACR Pediatric 70 response at the last study visit [17].

However, limiting assessment of efficacy is the fact that we do not currently have a standard outcome measure such as the DAS or CHAQ included in our electronic record to more objectively measure responses, nor do we routinely track patient-parent or MD global assessment of disease activity. However, all patients are seen by one of two providers (Physician or mid-level) at all visits, and we can therefore reduce the bias and improve reliability of physical exam findings. Another limitation is the relatively small number of patients included for review. It should be noted that this is further exacerbated by the inclusion of rarer diseases where only one patient is represented that diagnosis, such as with Blau's Syndrome. However, we felt it important to include these patients as well as the primary outcome we wished to explore was the safety of these agents in use in children with autoimmune or inflammatory disorders. It is unlikely any SAE was overlooked, as 99% of our patients charts are in one electronic medical record system. These patients also maintain routine follow up and contact our office with any events, documented with telephone encounter notes. Additionally, any admissions to the hospital or emergency department are reported to our service.

The value of this report is that we have a number of inflammatory childhood diseases included and have shown potential efficacy and importantly, safety of this treatment approach in a set of difficult to treat diseases, particularly those with few effective alternative therapies currently available. Furthermore, several different agents were shown

to be safe in this patient population. Other studies have shown similarly reassuring results in regards to the safety of using high dose biologics [5,6] and we believe that additional study is needed to affirm this treatment approach in recalcitrant disease states. Despite the limitations acknowledged, we did observe improvement in this group of patients with serious disease or previously unresponsive to standard dose therapy. Larger prospective randomized controlled studies are needed to further evaluate the safety and efficacy of this treatment.

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