Successful treatment with infliximab after adalimumab failure in pediatric noninfectious uveitis

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PURPOSE To describe the use of infliximab after adalimumab failure in the treatment of pediatric noninfectious uveitis.

METHODS A retrospective analysis was performed on the medical records of pediatric patients with noninfectious uveitis treated with infliximab for a minimum of 6 months after previously failing to achieve steroid-free remission using adalimumab at the University of Texas Medical School and Children's Medical Center between September 2015 and March 2018. Rates of achieving disease activity quiescence and steroid-free remission as well as incidence of adverse events were calculated.

RESULTS A total of 13 patients with noninfectious uveitis refractory to treatment with adalimumab met inclusion criteria. Three (23%) had anterior uveitis, 4 (31%) had pars planitis, and 6 (46%) had panuveitis. Eleven (85%) patients had preexisting ocular comorbidities. Of these, 4 (31%) had retinal vasculitis, and 1 (7.7%) had cystoid macular edema. There was a 100% response rate to treatment with infliximab following failure to achieve disease quiescence on adalimumab. At mean follow-up time of 21 months (range, 8-31) from initiation of infliximab, there was a reduction in steroid dependence from 100% to 15% after transitioning from adalimumab to infliximab ($P < 0.001$). Nine patients (69%) had achieved steroid-free remission on infliximab therapy. The mean time to steroid-free remission was 8.7 months.

CONCLUSIONS In our study cohort, infliximab was used successfully in all cases of recalcitrant pediatric noninfectious uveitis that previously failed adalimumab therapy. (J AAPOS 2019;23: 151.e1-5)

Uveitis is associated with high visual morbidity in pediatric patients, because this population typically presents later and with more intense, chronic intraocular inflammation than adults.[1] Corticosteroid use is typically a short-term treatment because of adverse effects associated with prolonged administration, including cushingoid features, growth restriction, weight gain, elevated systemic blood pressure, osteoporosis, gastrointestinal abnormalities, psychosis, and electrolyte imbalances.[1,2] Ocular toxicity from chronic steroid use in children includes cataracts, ocular hypertension, glaucoma, and amblyopia.[2-4]

Long-term control of uveitis may require steroid-sparing immunomodulatory therapy. In recalcitrant cases where the risk for vision loss is high or where first-line therapy (often an antimetabolite such as methotrexate), anti-tumor necrosis alpha (anti-TNFα) agents, such as infliximab and adalimumab, may be useful rescue agents.[3,4] The current body of literature lacks large-scale head-to-head studies between adalimumab and infliximab, and the superiority of either drug, or the ability of one to "rescue" patients failing the other, is inconclusive. The purpose of this study was to investigate the efficacy of infliximab in cases of pediatric noninfectious uveitis previously failing adalimumab.

Subjects and Methods

This study was approved by the Institutional Review Board at the University of Texas Medical School and Children's Medical

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Center, and our research methods adhered to the tenets of the Declaration of Helsinki and were compliant with the US Health Insurance Portability and Accountability Act of 1996.

The medical records of the pediatric patients with noninfectious uveitis treated at Children's Medical Center and University of Texas Southwestern Medical Center, Dallas, were reviewed retrospectively. Patients with chronic noninfectious uveitis who were evaluated by a single fellowship-trained uveitis specialist (JHC) between September 2015 and March 2018 and had a minimum of 6 months' follow-up were identified; those with noninfectious autoimmune uveitis who failed to achieve sustained control of ocular inflammation on adalimumab and were transitioned to infliximab infusions were included in our analysis. Patients not seen for more than 3 visits over the study interval or who had ocular inflammation secondary to infectious and malignant etiologies were excluded.

The following data were collected: demographics (age, race, sex), disease diagnosis, laterality, presence of ocular comorbidities (retinal vasculitis, cystoid macular edema, ocular hypertension/glaucoma, history of cataracts, monocular status, visual acuity), systemic disease association, duration of therapy, adverse reactions, and ability to achieve steroid-free remission.

A single fellowship-trained uveitis provider (JHC) personally examined and directly managed all treatment in accordance with previously described practice patterns.[5] Prior to switching to infliximab, all patients were on maximal doses of adalimumab (40 mg weekly) and an antimetabolite for a minimum of 3 months. Adalimumab was discontinued at the time of infliximab initiation. Infliximab was dosed at 5 mg/kg at 0 weeks, 2 weeks, and every 4 weeks thereafter. In cases where active uveitis persisted at infliximab 5 mg/kg every 4 weeks, the infliximab dose was increased incrementally by 2.5 mg/kg, with reassessment at the third infusion and escalation as needed until disease remission was achieved. Next, steroids were slowly tapered to extinction, and then the weekly infliximab intervals were extended in 1- to 2-week intervals, carefully ensuring steroid-free remission for a minimum of 3 months before each interval change. It was the practice pattern of the uveitis provider that all patients used concomitant antimetabolite (methotrexate) in conjunction with infliximab.

Uveitis was classified anatomically according to Standardization of Uveitis Nomenclature (SUN).[5,6] Response rate was defined by any clinical improvement on examination according to the SUN classification as well as improvement in any vasculitis on fluorescein angiography, when applicable. Disease remission was defined as less than grade 0.5+ anterior chamber cell, with absence of haze and no other clinical findings suggestive of disease activity based on dilated fundus examination. Remission was confirmed by the lack of activity on fluorescein angiography when intermediate or posterior involvement was suspected or previously documented. Steroid-free remission was defined as disease remission in the absence of use of corticosteroid therapy in any form (topical, periocular, oral, intravenous, or otherwise) for >90 days. Patients with steroid use in the perioperative period (typically cataract surgery) remained in the steroid-free remission category only if they had had a minimum of 90 days of steroid-free remission prior to surgery and had discontinued steroids within 90 days postoperatively. Time to steroid-free remission was defined as the interval between the initiation of infliximab infusions to the cessation of steroid use of any form.[5]

Statistical analyses were performed using SPSS 25.0 (SPSS Inc, Chicago, IL). The Fisher exact test, χ^2 analysis, binary logistic regression, and paired t tests were used to identify statistically significant relationships between variables and remission rates within our study cohort.

Results

Of 132 pediatric uveitis cases reviewed, a total of 13 patients met inclusion criteria. The mean follow-up interval was 21 months (range, 8-31). Table 1 provides the profile of our study cohort. There was a strong representation of Hispanic patients in this cohort. The mean age was 13 years (range, 8-18). Eleven patients (85%) had preexisting ocular comorbidities. All 13 patients had bilateral involvement of uveitis. Study demographics are summarized in Table 2. There were no statistically significant associations between achievement of steroid-free remission and demographic data and ocular comorbidities.

The average number of failed immunomodulatory therapies used prior to infliximab was 2.2 (range, 2-3), and included methotrexate (13), mycophenolate mofetil (1), and adalimumab (13). Average time on methotrexate was 5.9 years (range, 3.2-11.2). Average time on adalimumab was 2.7 years (range, 0.5-5.6). All patients were on concomitant corticosteroids prior to being transitioned from adalimumab to infliximab.

There was a 100% response rate to treatment with infliximab following failure to achieve disease quiescence on adalimumab. There was a reduction in the number of patients with persistent steroid dependence from 100% to 15% after transitioning from adalimumab to infliximab ($P < 0.001$). Eleven patients (85%) were on concomitant methotrexate and 2 (15%) were on concomitant mycophenolate mofetil. No patient with systemic manifestations suffered continued systemic symptoms while in ocular steroid-free remission.

The mean follow-up was 21 months (range, 8-31) from the start of infliximab infusions to the end of the study period. In this cohort, 9 patients (69%) achieved steroid-free remission on infliximab therapy. Of these, all but one (11%) maintained steroid-free remission to date. The single outlier patient's relapse was attributed to discontinuation of all immunomodulatory therapy while being lost to follow-up.

The average time to steroid-free remission was 8.6 months (range, 1-20), with 6 of these patients (46%) achieving steroid-free remission within 8 months. Of the patients who achieved steroid-free remission, infliximab dosing was 5 mg/kg in 4 (30%), 7.5 mg/kg in 3 (23%), and 10 mg/kg in 1 (7.7%). Although the maximal dose of infliximab for uveitis has been reported to be 20 mg/kg every 4 weeks,[7] none of our cohort required doses above

Table 1. Thirteen patients were treated with infliximab after adalimumab failure

Case	Age, years	Sex	Race	Ocular diagnosis	Retinal vasculitis (Y/N)	Systemic diagnosis	Other failed therapies	IFX dose	Response (Y/N)	Steroid-free remission (Y/N)
1	17	F	Black	Panuveitis	Y	Neurosarcoid	Ibuprofen, MTX, ADA	5 mg/kg q4wk	Y	Y
2	17	M	Hispanic	Pars planitis	Y	—	MTX, ADA	5 mg/kg q4wk	Y	N
3	9	M	Hispanic	Pars planitis	N	—	MTX, ADA	5 mg/kg q6wk	Y	Y
4	16	F	Asian	Panuveitis	Y	—	MTX, ADA	5 mg/kg q6wk	Y	Y
5	8	M	Hispanic	Panuveitis	N	—	MMF, MTX, ADA	10 mg/kg q4wk	Y	Y
6	11	F	Hispanic	Pars planitis	Y	—	MTX, ADA	7.5 mg/kg q6wk	Y	Y
7	17	F	Hispanic	Anterior uveitis	N	JIA	MTX, ADA	7.5 mg/kg q6wk	Y	Y
8	10	M	Hispanic	Panuveitis	N	—	MTX, ADA	7.5 mg/kg q4wk	Y	N
9	18	M	Black	Anterior uveitis	N	JIA, HLA B27	MTX, ADA	5 mg/kg q4wk	Y	Y
10	8	F	White	Anterior uveitis	N	JIA	MTX, ADA	7.5 mg/kg q4wk	Y	N
11	12	F	Black	Panuveitis	N	JIA	MTX, ADA	7.5 mg/kg q4wk	Y	Y
12	12	F	Hispanic	Panuveitis	N	JIA	MMF, MTX, ADA	7.5 mg/kg q4wk	Y	N
13	8	F	Black	Pars planitis	N	—	MTX, ADA	7.5 mg/kg q4wk	Y	Y

ADA, adalimumab; *IFX*, infliximab; *JIA*, juvenile idiopathic arthritis; *MMF*, mycophenolate; *MTX*, methotrexate.

Table 2. Patient demographics and baseline characteristics[a]

Demographic/clinical trait	No. (%)
Age, years	
<12	6 (46)
≥12	7 (53)
Sex	
Male	5 (38)
Female	8 (61)
Race	
White	1 (7.7)
Black	4 (31)
Hispanic	7 (54)
Asian	1 (7.7)
Ocular diagnosis	
Panuveitis	6 (46)
Pars planitis	4 (31)
Anterior uveitis	3 (23)
Ocular comorbidity	
Retinal vasculitis	4 (31)
Macular edema	1 (7.7)
Cataract	11 (85)
Ocular hypertension	1 (7.7)
Glaucoma	5 (38)
Monocular status	6 (46)
Systemic autoimmune disease	
Overall	6 (46)
Neurosarcoidosis	1 (7.7)
Juvenile idiopathic arthritis	5 (38)
HLA B27 spondyloarthropathy	1 (7.7)
None	7 (54)

[a]There were no statistically significant relationships between the demographic factors and the ability to achieve steroid-free remission, in pediatric noninfectious uveitis patients who were on infliximab infusions after failing adalimumab.

10 mg/kg every 4 weeks. Infliximab infusion interval varied from 4 to 10 weeks, with an average of 5.2 weeks. Four patients (29%) required at least 8 monthly infusions before achieving disease remission and initiation of corticosteroid taper. The remaining 2 patients (15%) who remained on corticosteroid therapy were in the midst of a corticosteroid taper. Time to steroid-free remission is illustrated in Figure 1. There were no serious adverse events that required cessation of infliximab. There was one episode of asymptomatic bradycardia and hypotension, which resolved with the elimination of diphenhydramine premedication to the infusion protocol.

Discussion

This study reports 100% improvement in uveitic control of noninfectious uveitis when switching to infliximab after previously failing adalimumab. Furthermore, 69% of these patients were able to achieve steroid-remission on infliximab despite previously failing adalimumab. Infliximab was generally well tolerated, with no significant adverse reaction requiring treatment cessation in our cohort. Our cohort had a predominance of Hispanic patients, a subpopulation that is not well represented in previous studies. We were able to achieve similar positive response rates in this cohort, suggesting that Hispanic ethnicity may not significantly affect response to infliximab.

Biochemically, TNFα blockade is thought to exert its beneficial effects through downregulation of inflammatory cytokines (including IL-1, IL-2, and IL-6), endothelial adhesion molecules, T-cells, and macrophages.[3,8,9] Adalimumab, a subcutaneously administered recombinant human IgG1-kappa monoclonal antibody against soluble and receptor-bound TNFα, is the first nonsteroid agent approved by the Food and Drug Administration for the management of noninfectious uveitis in adults.[4,9] Retrospective analyses have reported success rates of 47%-77%.[2-4,10] Infliximab is a chimeric human-mouse monoclonal G1 immunoglobulin targeting both the membrane-bound and soluble forms of TNFα that has also shown promise with success rates of 0%-95% in retrospective studies.[8,11-13]

There is currently lack of consensus of the efficacy of adalimumab versus infliximab in achieving inflammatory control.[14-18] The mechanism underlying the apparent success of one anti-TNFα agent over another in refractory cases of noninfectious uveitis is likely multifactorial, but it may include epigenetic factors,

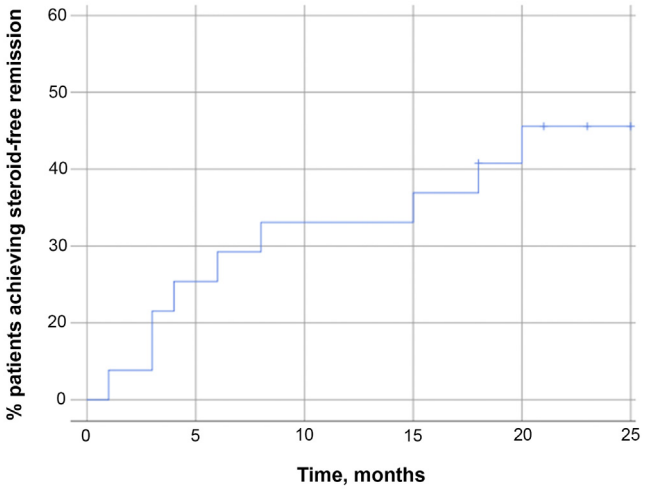

FIG 1. Time to steroid-free remission: this Kaplan-Meier curve illustrates the time it took pediatric noninfectious uveitis patients to achieve steroid-free remission on infliximab infusions following adalimumab failure.

biochemical differences, and characteristics unique to each case. It has been suggested that superiority of one anti-TNFα agent versus another may also vary with specific systemic disease associations.[19-21]

There are also unique logistical aspects in cost and administration that may influence the decision to initiate adalimumab versus infliximab. Adalimumab can be an effective modality for those wishing to complete all therapy in the home environment.[22] However, anxiety associated with medication administration is a significant limiting factor for initiation of and compliance with the medication,[23] particularly in children. Infliximab has a quicker onset of action and wider dosing customization. However, the risk of infusion reactions, increased "chair time" requiring missed school days, and barriers to insurance approval for its off-label use in uveitis are all considerations in the decision to use infliximab as a therapeutic option in pediatric uveitis.[14,22] In light of increased clinical interest in the efficacy of switching between different anti- TNFα agents in refractory cases, entertaining the use of infliximab after failure of adalimumab is not an unusual clinical practice. However, literature regarding the use of infliximab following adalimumab failure is lacking.

Notably, as corroborated by previous reports,[7,24] a considerable number of patients in our cohort required higher and more frequent ("uveitic") doses of infliximab than introductory "rheumatologic" dosing, in which infliximab is extended to every 6 weeks after one monthly dose. All patients in our cohort were initiated on 5 mg/kg monthly, with 7 (54%) escalating to 7.5 mg/kg dosing and 1 (7.7%) to 10 mg/kg dosing. Four patients (31%) required at least 8 monthly infusions before achieving disease remission. This result underscores the need for the prescribing ophthalmologist to delve into detail with the prescriber of infliximab (typically a uveitis specialist or coordinating rheumatologist) to differentiate insufficient dosing and/or premature extension of infliximab from true infliximab failure.

Previous large studies comparing the effect of adalimumab and infliximab in childhood refractory chronic uveitis demonstrate similar positive results in favor of both agents.[25,26] The route of medication administration between the two anti-TNFα agents may have biased the cohort of patients included in our study; those with severe intolerance to subcutaneous injections of methotrexate, families with poor compliance, and more severe cases of uveitis often chose infliximab as initial therapy. Therefore, there may be some implicit bias, with milder cases of uveitis being selected for trial with adalimumab before initiating infliximab (and therefore included in our study) as opposed to initiating infliximab first. Additionally, compliance with immunomodulatory therapy may present some variability in outcomes.

Future larger, long-term prospective studies will be needed to confirm our results, determine effect on visual outcomes, and to identify whether there are specific positive prognostic factors for successful infliximab rescue in a nonspecific cohort of chronic uveitis patients that have failed a trial of adalimumab. Notwithstanding these limitations, our study contributes to a growing body of evidence that infliximab can be an effective treatment modality for noninfectious uveitis. In our cohort of patients, there was a 100% response rate, an 85% reduction in steroid dependence, and a 69% success rate in achieving steroid-free remission.

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