

ADALIMUMAB THERAPY FOR CHILDHOOD UVEITIS

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Fourteen children with uveitis (9 JIA associated and 5 idiopathic) were treated with adalimumab for an average of 18.1 months. Inflammation decreased in 21/26 eyes (80.8%), 4 eyes remained stable (15.4%), and 1 worsened (3.8%) ($P < .001$; 2 tailed paired Wilcoxon rank sum test). No significant adverse events occurred. (*J Pediatr* 2006;149:572-5)

Most childhood uveitis is idiopathic. Juvenile idiopathic arthritis (JIA) is the most commonly associated systemic disease in childhood, occurring in 14.9% of cases.¹⁻³ Antinuclear antibody (ANA)-positive girls <10 years of age with oligoarticular JIA are at the greatest risk of developing eye disease.⁴

The sera and aqueous humor of patients with uveitis contain increased amounts of tumor necrosis factor (TNF) α , suggesting it is a key mediator of uveal inflammation.⁵ Inhibition of TNF α with a p55 TNF α receptor fusion protein ameliorates intraocular inflammation in experimental autoimmune uveitis.⁶ However, etanercept and infliximab have failed to demonstrate consistent efficacy in the treatment of ocular inflammation.⁷⁻¹⁶ A randomized, placebo-controlled trial using etanercept in the treatment of JIA-associated uveitis failed to show any difference between etanercept and placebo therapy.¹⁶

Adalimumab is a recombinant human immunoglobulin G1 monoclonal antibody that binds specifically to TNF α and blocks interaction with the p55 and p75 cell surface receptors. We hypothesized that this monoclonal antibody would be more effective in suppressing inflammation than etanercept, which is a synthetic receptor for TNF α and does not act against cell-bound TNF. Adalimumab was used on a weekly administration schedule that provides better sustained levels of anti-TNF α activity than infliximab, which is administered as periodic intravenous infusions.¹⁷ We have successfully treated 14 children with idiopathic (5 children) or JIA-associated (9 children) uveitis with adalimumab in a prospective open-label evaluation.

METHODS

Fourteen children with either idiopathic or JIA-associated uveitis attending rheumatic disease clinics at the Hospital for Special Surgery between January 2003 and May 2005 were prospectively offered adalimumab therapy. All had uveitis poorly responsive to standard therapy (11 children) or inadequately controlled arthritis that we elected to treat with adalimumab while they were concurrently experiencing uveitis (3 children). In all cases of idiopathic uveitis a thorough ophthalmologic evaluation was performed by the ophthalmologists and a complete serologic evaluation and physical examination were performed by the pediatric rheumatologist to eliminate other diagnoses including Behcet's, sarcoid, and infectious etiologies. The risks and benefits of adalimumab and alternative therapies were explained, and informed consent was obtained in all cases.

Adalimumab was administered to all patients by injection at a dose of 40 mg/M²/week, with a maximum dose of 40 mg once each week. For children who were <0.5M², 40 mg (or less as appropriate to size) once every 2 weeks was given. This is the customary dose used for the treatment of children with multi-drug resistant JIA in our institution, as most patients referred for treatment of their arthritis have previously failed other anti-TNF agents. The same dosage was used to treat the children with uveitis on an empiric basis.

Changes in ocular inflammation (cells or flare), intra-ocular pressure, visual acuity, and concurrent medications were recorded at each ophthalmologist visit. All children were seen by one of two collaborating ophthalmologists, and all children saw the same ophthalmologist at each visit. Cellular flare in the anterior chamber and visual acuity were recorded every 3 months from the onset of treatment with adalimumab. Measurement of cellular flare in the anterior chamber was made by the same ophthalmologist using standard techniques,¹⁸ and all children were seen a minimum of every 4 weeks (more often when necessary). Improvement in cellular flare was defined as a sustained decrease in

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ANA	Antinuclear antibody	NSAIDs	Nonsteroidal anti-inflammatory drugs
JIA	juvenile idiopathic arthritis	TNF	Tumor necrosis factor

Table I. Demographic data

Patient	Age (y)	Indication	Sex	Diagnosis	ANA
1	11	Arthritis	M	JIA	Neg
2	19	Uveitis	F	JIA	Pos
3	9	Uveitis	F	Idiopathic	Neg
4	7	Arthritis	F	JIA	Neg
5	14	Uveitis	F	Idiopathic	Pos
6	8	Arthritis	F	JIA	Pos
7	13	Uveitis	F	JIA	Pos
8	14	Uveitis	M	JIA	Neg
9	13	Uveitis	M	Idiopathic	Neg
10	4	Uveitis	F	JIA	Pos
11	14	Uveitis	F	Idiopathic	Pos
12	14	Uveitis	F	Idiopathic	Neg
13	13	Uveitis	F	JIA	Pos
14	8	Uveitis	F	JIA	Pos

anterior chamber cell count over two visits 3 months apart. Improvement in visual acuity was defined as sustained improvement in the Snellen grade. Medication dosage, evidence of toxicity, and adverse events were monitored by the pediatric rheumatologist at the time of monthly examinations. All children had a monthly complete blood count, urine analysis, and routine chemistry profile.

Statistical Analysis

Statistical analysis was performed using the standard statistical functions in Graph Pad InStat (Graph Pad Software, Inc, San Diego, Calif). These tests included testing for the normality of the distribution of the results and Wilcoxon's rank sum nonparametric paired *t* tests. All results are reported as the mean \pm 1 standard error.

RESULTS

Patient Population

Fourteen children were treated (11 girls). Mean age at treatment onset was 11.5 years (range 4-19 years) (Table I). Five children had idiopathic uveitis and nine had JIA-associated uveitis (five oligoarticular, four polyarticular). Eight of 14 children (57.1%) were ANA positive (4/5 oligoarticular JIA [80%], 2/4 polyarticular JIA [50%], and 2/5 idiopathic [40%] uveitis); none were human leukocyte antigen (HLA) B 27 positive. Mean duration of treatment and follow-up was 18.1 \pm 2.3 months.

Ocular Involvement

Twenty-six eyes in 14 children were affected at initiation of therapy. Decreased anterior chamber cellular flare was observed in 21 of 26 affected eyes (80.8%), with 17 of 26 (65.3%) demonstrating sustained resolution of inflammation throughout the period of study (Table II). Four eyes remained stable (15.4%), whereas 1 of 26 eyes had an increase in inflammation (*P* < .0001, paired Wilcoxon's rank sum analysis). Ocular response was often dramatic and typically oc-

curred within the first 2 to 6 weeks of therapy. Median time to response was 6 weeks (range 2-12 weeks). All of the children were able to progressively taper at least one of their other medications, and no child required an increase in medications. The one eye that worsened did so as medication was tapered.

Visual Acuity

Improved visual acuity was noted in 10 of 26 affected eyes (seven patients), acuity remained stable at 20/20 in 9 eyes. Visual acuity remained stable but less than 20/20 in 6 eyes, and worsened in 1 eye during therapy (*P* < .0025 by paired Wilcoxon's rank sum analysis, two-tailed).

Other Medications

Topical corticosteroid drop use was decreased in 11 of 14 children (78.5%), including 4 of 14 (28.5%) who discontinued the drops completely. Oral steroids were discontinued in 2 of the 3 children who were taking them at the initiation of therapy, and the dosage was decreased in the remaining child.

Methotrexate was successfully discontinued in 2 of 11 children (18.2%) with 1 of 4 affected eyes showing increased visual acuity and 4 of 4 eyes having complete resolution of ocular inflammation. Nonsteroidal anti-inflammatory drugs (NSAIDs) used for either arthritis or uveitis were discontinued in 5 of 10 children (50%), visual acuity improved in 1 of 9 with resolution of inflammation in 8 of 9 affected eyes. Three of the 5 children (60%) were using cyclosporin A systemically and were able to discontinue the medication with improvement in visual acuity in 2 of 6, resolution of inflammation in 5 of 6, and decreased inflammation in all affected. Mycophenolate mofetil was decreased in 2 of 3 (66.7%) children with 3 of 4 affected eyes having complete resolution of inflammation, one of which had worsening visual acuity. Finally, azathioprine was discontinued in 2 of 2 (100%) children with no change in visual acuity and resolution of inflammation in 1 of 4 affected eyes. Two of the 14 patients (14.2%) were weaned off all other immunosuppressive medications and remain stable on adalimumab at 12 and 28 months of follow-up. Four of the 14 children (28.6%) have been able to decrease their adalimumab dosage by increasing the interval between injections without flare of their disease.

Adverse Events

Pain at the injection site was the only adverse event reported by patients. No severe reactions occurred that required discontinuation of adalimumab. One patient developed increased intraocular pressure during therapy secondary to glaucoma. This occurred despite a decrease in ocular inflammation in the affected eye. No significant laboratory abnormalities occurred in the complete blood count, comprehensive metabolic profile, or routine urine analysis.

Table II. Adalimumab treatment response

Patient	Pre Adal Tx medications	Visual acuity (OD/OS)	Cell flare	Post Adal Tx medications	Visual acuity	Cell flare	Duration of treatment (mo)
1	Pred forte	20/20	Tr	↓ Pred forte	20/20	0	9
	NSAIDs MTX	20/20	Tr	↓ MTX	20/20	0	
2	Pred forte oral steroid	20/25	1+	↓ Pred forte NSAIDs	20/20	Tr	25
	NSAIDs MTX	20/25	0	↓ Oral steroid MTX	20/20	Tr	
3	Pred forte	20/40	Tr	None	20/30	0	12
	Oral steroid MTX	20/20	Tr		20/20	0	
4	Pred forte CSA	20/30	Tr	↓ Pred forte	20/20	Tr	24
	NSAIDs MTX	20/50	Tr	NSAIDs MTX	20/25	0	
5	Pred forte	20/20	1+	MTX	20/20	0	4
	NSAIDs MTX	20/20	Tr		20/20	Tr	
6	Pred forte AZA	20/20	0	↓ Pred forte	20/15	0	26
	NSAIDs MTX	20/20	Tr	NSAIDs ↓ MTX	20/20	Tr	
7	Pred forte CSA	20/25	2+	↓ Pred forte	20/30	0	6
	MTX	20/100	3+	MTX	20/30	0	
8	Pred forte CSA	20/20	Tr	↓ Pred forte CSA	20/20	Tr	24
	NSAIDs MMF	20/25	1+	NSAIDs	20/40	Tr	
9	Pred forte	20/30	1+	MTX	20/25	0	8
	MTX	20/20	1+		20/20	0	
10	Pred forte	20/30	1+	↓ Pred forte	20/20	Tr	17
	NSAIDs MTX	20/30	1+	NSAIDs MTX	20/20	Tr	
11	Pred forte NSAIDs CSA	20/200	Tr	↓ Pred forte ↓ CSA	20/200	0	19
	Oral steroid MMF	20/60	Tr	MMF	20/30	0	
12	Pred forte	20/20	Tr	↓ Pred forte	20/15	0	24
	MTX	20/20	1+	↓ MTX	20/20	0	
13	Pred forte NSAIDs CSA	20/20	2+	↓ Pred forte	20/20	0	28
	MTX MMF	20/20	2+		20/20	0	
14	Pred forte NSAIDs AZA	20/20	1+	None	20/20	0	28
	Etanercept	20/20	0		20/20	0	

P values are for comparison of pre- and post-treatment values by Wilcoxon's rank sum test. Cell flare refers to cells in the anterior chamber or protein flare. AZA, azathioprine; CSA, cyclosporin A; MMF, mycophenolate mofetil; MTX, methotrexate; NSAIDs, nonsteroidal anti-inflammatory drugs; Tr, trace; Tx, treatment; ↓, dosage decrease.

DISCUSSION

Potential ocular complications of idiopathic and JIA-associated uveitis include band keratopathy, cataract, glaucoma, synechiae, and optic nerve edema. These complications may ultimately result in blindness.¹⁹ Therapy of uveitis typically follows a stepladder approach beginning with topical corticosteroid drops.²⁰ Although this often proves successful, some children do not respond adequately. Because prolonged use of corticosteroid drops is associated with an increased incidence of cataracts and glaucoma, alternative therapy is desirable.

Although one previous study reported that etanercept had some efficacy in the treatment of chronic uveitis in children,⁸ subsequent studies failed to demonstrate a benefit with respect to relapse or final visual acuity.^{9,16} Other reports demonstrate that uveitis may develop in children receiving anti TNF α therapy.²¹⁻²² One child in our cohort has had a sustained response to adalimumab after failing to respond to etanercept. Infliximab is effective for posterior uveitis associated with Behcet's syndrome,¹⁹ but the experience regarding children is limited to single case reports or series that include adults and children with a variety of diagnoses.¹⁴⁻¹⁵

Our results indicate that adalimumab may be a useful therapy for children with idiopathic and JIA-associated uveitis. We hypothesized that adalimumab would provide a superior response because it binds to TNF α on the cell surface and not just in the circulation. In addition weekly or biweekly administration provides a more consistent serum level than periodic infusions of infliximab. These may be important factors, but they were not directly addressed in this study. There was a decrease in ocular inflammation in 13 of 14 children with sustained response to therapy after a mean of 18 months of treatment and discontinuation or decreased dosage of other immunosuppressive agents in 13 of 14 children treated. All of these children were poorly responsive to conventional therapy for uveitis. A larger placebo-controlled trial is required to conclusively demonstrate the efficacy of adalimumab therapy for idiopathic and JIA-associated uveitis in childhood.

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