EXTENDED REPORT

Biological response modifier therapy for refractory childhood uveitis

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Purpose: To evaluate the use of biological response modifiers (BRM) in the treatment of refractory childhood uveitis.
Design: Retrospective non-comparative case series of pediatric patients with uveitis treated with BRM.
Participants: 23 pediatric patients.
Methods: All children (18 years or younger) who received a BRM were assessed for visual changes, time to control inflammation, and any associated adverse side effects. Thirteen patients were treated with infliximab, five with adalimumab, and five with daclizumab. All patients had bilateral eye involvement. Diagnoses of the participants included juvenile idiopathic arthritis, keratouveitis, sarcoid panuveitis, Adamantiades–Behcets disease, and idiopathic panuveitis.
Main outcome measures: Inflammation and visual acuity.
Results: In the infliximab group 16 of 26 eyes (62%), and 10 of 13 patients (77%) demonstrated an improvement in visual acuity. Twenty of 26 eyes (77%) demonstrated an improvement in the degree of inflammation. In the adalimumab group, four of 10 eyes (40%) demonstrated an improvement in visual acuity, with five of 10 eyes (50%) demonstrating an improvement in inflammation. Four of 10 eyes (40%) in the daclizumab group demonstrated an improvement in vision with eight of 10 eyes (80%) demonstrating an improvement in inflammation.
Conclusion: BRM appear to be safe to use in children, and represent a useful therapeutic adjunctive drug group for treating recalcitrant childhood uveitides.

Childhood uveitis is a relatively uncommon, but serious disease, with the potential for significant long-term morbidity.[1] Children with bilateral involvement or those who present with panuveitis usually require early aggressive systemic therapy to prevent visual loss and long-term complications. The approach to a child with refractory or initial onset aggressive uveitis is a therapeutic challenge that necessitates weighing the risks of blindness and the inherent complications of persistent ongoing inflammation with the toxicity of immunomodulatory and cytotoxic therapy.

The mainstay of initial therapy for severe forms of bilateral uveitis is corticosteroids.[2] Chronic administration of corticosteroids, however, is associated with significant morbidity in this age group. Some of the more serious adverse effects include suppression of the hypothalamic–pituitary–adrenal axis, osteoporosis, aseptic necrosis of bone, growth retardation, secondary infections, and behavioral disturbances resulting in potential devastating physical and emotional dysfunction.[3]

Refractory uveitides in childhood require adjunctive immunomodulatory therapy. Many agents (antimetabolites, alkylating agents and T-cell inhibitors) have been trialled with variable success and each has significant potential toxicity.[4–9]

Contemporary management of patients with recalcitrant ocular inflammation includes the treatment option of biological response modifiers (BRM). These agents can be broadly defined, but generally include monoclonal antibodies directed against selected cell surface glycoproteins, or recombinant forms of natural inhibitory molecules.[10] Tumor necrosis factor alpha is a cytokine that has been implicated in the pathosis of many autoimmune diseases. Earlier experimental studies have demonstrated that anterior segment inflammation induced in Lewis rats by systemic injection of lipopolysaccharide is associated with the early production of this cytokine,[11] and that tumor necrosis factor alpha has been demonstrated in the aqueous humor and serum of patients with uveitis.[12] Therapeutic trials have demonstrated the efficacy of blockade of this cytokine in the treatment of several diseases.[13 14] Preliminary clinical reports suggest a favorable effect of infliximab and adalimumab for the treatment of uveitis in childhood.[15–18]

Daclizumab (Zenapax; Hoffman-LaRoche, Inc., Nutley, New Jersey, USA) is a humanized immunoglobulin G monoclonal antibody produced by recombinant DNA technology that specifically binds CD25 of the human interleukin 2 receptor that is expressed on activated T lymphocytes. Nussenblatt and colleagues[19] have demonstrated the safety and efficacy of daclizumab in adult patients with uveitis, and demonstrate that in most cases it may reduce the concomitant immunosuppressive burden required to treat non-infectious uveitis.[20] There is a distinct lack of data regarding the use of this drug in children. We reported treatment with daclizumab[21] in a cohort of patients that included a subgroup of six children, three of which demonstrated an improvement in inflammation, whereas no patient incurred an adverse reaction to the medication.

We report the experience at Massachusetts Eye Research and Surgery Institute, on the use of BRM for the treatment of childhood uveitis that was resistant to more conventional anti-inflammatory or immunomodulatory therapy.

MATERIALS AND METHODS

Design

A retrospective chart review was performed on all pediatric patients with chronic, refractory ocular inflammation who were

Abbreviation: BRM, Biological response modifier

treated with a BRM. The agents included adalimumab, infliximab, and daclizumab. The purpose of this study is to describe our experience on the matter of efficacy and safety with these agents as adjunctive therapy in recalcitrant ocular inflammatory disease.

Eligibility

Any patient who started a BRM at age 18 years or younger was included in this series. Inclusion criterion was that the patient had previously failed or was intolerant to standard therapy used to treat uveitis. Failure of therapy was defined as uncontrolled or worsening inflammation despite therapy with at least one immunosuppressive agent, as well as corticosteroids.

Procedure

Patients who met our inclusion criterion were included in the study. If the patient agreed to proceed with treatment, the risks, benefits, and alternatives to BRM therapy were explained. Baseline complete blood count, liver function, blood urea nitrogen, and serum creatinine level were obtained along with a complete medical history and review of systems.

Medical records were reviewed after obtaining Institutional Review Board approval. Demographic data, including age, gender, type of uveitis, and systemic diagnosis was recorded and are listed in table 1.

The choice of BRM for each patient was based on clinical considerations. All agents were prescribed by the same ocular immunologist (C.S.F.) or by the patient's rheumatologist. Subcutaneous adalimumab was administered at a dose of 40 mg/M^2 every other week.

Infliximab infusions (range 100–700 mg) were initially given at two-week intervals and then continued at four to eight-week intervals. Daclizumab was administered intravenously at a dose of 1 mg/kg per treatment, (range, 25 mg–75 mg) at frequencies ranging from every 2 to 8 weeks. Any previous immunomodulatory treatments used, concomitant therapy, or adverse effects to the BRM's were recorded and were documented in table 2.

At each visit (four to six-week intervals), history (including the dosage and frequency of all topical and systemic medications) was recorded and an ophthalmological examination was conducted. This included vision and intraocular pressure measurement as well as an assessment of intraocular inflammation by using slitlamp examination and dilated funduscopic examination. The degree of inflammation was graded using the standards described in Foster and Vitale's ''Diagnosis and treatment of uveitis''.[22] Anterior chamber cells and flare were graded between 0 and 4 in 0.5 gradations, with 0.5 or less considered inactive.Vitritis, evidenced by the presence of cells, not haze, was also graded from 0 to 4 and considered inactive when there were 0.5 cells or less.

Inflammation of the retina and choroid was documented by the presence of retinal vasculitis, cystoid macula edema, chorioretinitis, or papillitis. An improvement in inflammation was reported as a decrease of anterior or posterior segment inflammation by one or more grades. A relapse in inflammatory control was defined as an increase in cellular activity by 1+ cells or more. An improvement in visual acuity was defined as a sustained improvement in the Snellen grade of one or more lines. Patient's visual acuities and degree of inflammation are documented in table 1.

Complete blood count, liver function, blood urea nitrogen, and serum creatinine levels were obtained and reviewed at four to six-week intervals. Patients were only discontinued BRM therapy if they developed an adverse event, were lost to follow-up, were non-compliant, withdrew voluntarily or failed to go into remission.

RESULTS

Twenty-three patients were treated with a BRM (18 females and five males). The average patient age was 11.2 years (range four to 18 years). The average treatment duration was 16.9 months (range 1.3–54.1 months).

Five patients were treated with adalimumab (four females and one male). The average duration of treatment was 9.3 months (range 1.3–26 months). The mean time to control inflammation was 3.9 weeks (range 1.7–8.6 weeks). Four of these patients had a diagnosis of juvenile idiopathic arthritis, and one had Adamantiades–Behcets disease. In the adalimumab group four of 10 eyes (40%) demonstrated an improvement in visual acuity. Two of 10 eyes retained stable visual acuity and four of 10 eyes demonstrated deterioration in

Table 1 General demographics, visual outcomes and degree of inflammation

Patient	Gender	Age at initiation of therapy	Diagnosis	Drug	BCVA initial	BCVA final	Degree of inflammation	Degree of inflammation	Treatment duration (months)
1	M	6	JIA-U	Adalimumab	20/20	20/15	1+	Quiet	3
2	F	16	JIA-U	Adalimumab	20/50	20/40	3+	Quiet	8.2
3	F	10	JIA-U	Adalimumab	20/20	20/20	2.5+	1.5+	1.3
4	F	13	ABD	Adalimumab	20/20	20/20	1+	Quiet	26
5	F	4	JIA-U	Adalimumab	20/20	20/25	3+	1+	8.2
6	F	11	JIA-U	Infliximab	20/20	20/20	1+	1+	12
7	M	7	JIA-U	Infliximab	20/20	20/20	3+	1+	8.6
8	F	4	JIA-U	Infliximab	20/60	20/20	1.5+	Quiet	9.5
9	F	17	JIA-U	Infliximab	20/25	20/20	Quiet	Quiet	16.8
10	F	5	JIA-U	Infliximab	20/25	20/15	3+	Quiet	5.1
11	F	11	JIA-U	Infliximab	20/20	20/20	1+	Quiet	17.1
12	F	14	JIA-U	Infliximab	20/30	20/20	Quiet	Quiet	26.9
13	F	6	JIA-U	Infliximab	20/20	20/20	1+	Quiet	22
14	F	15	JIA-U	Infliximab	20/30	20/20	Quiet	1+	50.8
15	F	6	JIA-U	Infliximab	20/20	20/20	3+	Quiet	5.1
16	F	18	JIA-U	Infliximab	20/20	20/15	4+	Quiet	9
17	M	6	JIA-U	Infliximab	20/20	20/20	4+	1+	30
18	M	11	JIA-U	Infliximab	20/15	20/15	2+	1+	5.7
19	F	8	Keratouveitis*	Daclizumab	20/30	20/20	4+	Quiet	54.1
20	M	12	Sarcoidosis†	Daclizumab	20/25	20/25	3+	Quiet	30.9
21	F	18	Anterior uveitis*	Daclizumab	20/25	20/25	3+	Quiet	14.5
22	F	12	Sarcoidosis†	Daclizumab	20/20	20/20	1+	Quiet	14.6
23	F	17	Panuveitis*	Daclizumab	20/20	20/20	3+	1+	10.5

BCVA, Best corrected visual acuity; JIA-U, juvenile idiopathic arthritis-associated uveitis; Adamantiades–Behçet's disease.
*Idiopathic; †panuveitis.

Table 2 Immunomodulatory therapy

Patient	Previous IMT	Concomitant medication	Time to control inflammation (weeks)	Adverse effects	Treatment status
1	MM, MTX, INF	MM, MTX, CLX, PF	2	None	Ongoing
2	MTX, ETP	MTX, PF	3.3	None	Ongoing
3	MM, MTX, CSA, ETP	MM	4.3	None	Ongoing
4	MTX, CSA	CSA, PF	1.7	None	Ongoing
5	MTX, ETP	MTX, MM, PF	8.6	None	Ongoing
6	MM, CSA	PF, BFC	4.7	Elevated LFT*	Ongoing
7	MTX	MM, PF	3.7	Nausea	Discontinued
8	None	MTX, PF	20	Elevated LFT*	Ongoing
9	MTX	MM, PF	45	None	Ongoing
10	MTX	MM	2	None	Ongoing
11	MM	MTX, PRED, PF, BFC	5.9	None	Ongoing
12	None	MTX, PF	7	None	Remission
13	MTX	MM, LE	7.3	None	Ongoing
14	CSA, MM	PF	4.3	None	Ongoing
15	MTX, MM	MTX, MM, PF	9.7	None	Ongoing
16	MM, ETP	MM, PF	4.3	Leukopenia*	Ongoing
17	MTX, CHL	MTX, MEL	5.3	None	Ongoing
18	MTX, ETP	MM, CSA, PF, ATO	12.3	None	Ongoing
19	MTX, CSA, AZA	RIM	25	Leukopenia*	Remission
20	MTX, CSA, MM, CHL	PF, IV MPD	46.3	Fatigue, myalgia	Remission
21	MM, CSA, SIR	MM, CSA, SIR, PF	6.4	Nausea	Ongoing
22	MTX, MM	MM, PRED, PF, BFC	8	Leukopenia*	Ongoing
23	MTX, MM, CSA	None	3.4	Leukopenia*	Ongoing

ATO, Atropine 1% drops; AZA, azathioprine; BFC, bromfenac 0.09%; CHL, chlorambucil; CLX, celecoxib; CSA, cyclosporine; ETP, etanercept; INF, infliximab; IV MPD, intravenous methylprednosolone; LE, loteprednol etabonate 0.5% drops; LFT, liver function test; MEL, meloxicam; MM, mycophenolate mofetil; MTX, methotrexate; PF, prednisolone 1%; PRED, oral prednisone; RIM, rimexolone 1%, SIR, sirolimus.
*Transient.

vision. With respect to inflammation, five of 10 eyes (50%) demonstrated an improvement, with three of 10 eyes (30%) remaining stable and two of 10 eyes (20%) deteriorating. Overall, two patients improved on therapy, two remained stable and one patient deteriorated clinically. There were no serious adverse effects recorded for this group.

Thirteen patients were treated with infliximab (10 female and three male). The average duration of treatment was 16.8 months (range 5–50 months). The mean time to control uveitis was 10 weeks (range 3.7–44.9 weeks). All 13 patients treated with infliximab had a diagnosis of juvenile idiopathic arthritis. Sixteen of 26 eyes (62%) demonstrated an improvement in vision, with eight of 26 eyes (31%) remaining stable. Two of 26 eyes (8%) demonstrated a visual deterioration. With respect to inflammation, 20 of 26 eyes (77%) demonstrated an improvement, four of 26 eyes (15%) remained stable and two of 26 eyes (8%) deteriorated. Overall, 10 patients improved on therapy whereas three remained stable. Two of these patients developed elevated liver function enzymes, one described nausea, and one had a transient leucopenia.

Five patients were treated with daclizumab (four female and one male). The average duration of treatment was 24.9 months (range 10–54 months). The mean time to control inflammation was 18 weeks (range 3–46 weeks). Two of these patients had a diagnosis of sarcoid uveitis, one had keratouveitis, one had idiopathic anterior uveitis and one had idiopathic panuveitis. Four of 10 eyes (40%) demonstrated an improvement in visual acuity. Five of 10 eyes (50%), remained stable whereas one of 10 eyes (10%) demonstrated a deterioration in vision. With respect to inflammation, four of 10 eyes (40%) demonstrated an improvement, five of 10 eyes (50%) remained stable, with only one of 10 eyes (10%) demonstrating a deterioration. Overall, three patients improved on therapy whereas two remained stable. Three of these patients incurred transient leucopenia, one described nausea and one patient related fatigue and myalgia.

DISCUSSION

Our results suggest that BRM may be a safe and efficacious treatment choice in children with manifestations of refractory uveitides. We acknowledge that there are multiple sources of bias that preclude drawing definite conclusions. The small sample sizes in all three treatment groups limit the power of this study. The inherent selection bias of a tertiary referral center must be taken into account as these children represent the more severe side of the disease spectrum. The diseases treated in this study represent a heterogeneous group and therefore will have variable responses to treatment. Furthermore, as the therapy was tailored for each patient, there are underlying discrepancies in the dosing intervals and duration because of underlying differences in the cause of disease and concomitant immunomodulatory therapy. Finally, of course, the experience was not one of a prospective, randomised, masked and controlled clinical trial. We can, however, deduce some overall observations that are useful because there is a definite paucity of reports of BRM use for childhood uveitides in the world literature.

All of our patients, except three (patient nos. 11, 20, and 22), have been successfully discontinued from systemic prednisone. These three patients were receiving corticosteroids for flare-ups. The flare-up rate in this study group was 40%. Three patients were induced into remission, one with infliximab therapy, and two with daclizumab therapy. Three of the infliximab patients with arthritis were also commenced on treatment for their rheumatological symptoms but their ocular state remained stable on treatment.

Our observations in relation to the use of infliximab concur with the two small series published in 2006. Rajaraman and colleagues[15] demonstrated that their six patients had control of their intraocular inflammation; the only adverse reactions seen were the development of a vitreous hemorrhage in one patient and a case of transient upper respiratory infusion reaction in another. Kahn and colleagues,[16] in their report of 17 children who were administered high-dose infliximab for the treatment of chronic uveitis, related that the treatment was rapidly effective and well tolerated with no serious adverse effects reported.

Reports on the use of adalimumab in the treatment of childhood uveitis are also scarce. Vazquez-Cobian and colleagues[17]

reported the use of adalimumab in 14 children with either idiopathic or juvenile idiopathic uveitis and relate a decrease in inflammation in 21 of 26 eyes (80.8%). They reported no significant adverse effects to treatment. Beister and colleagues,[18] in their report of 18 patients treated with adalimumab, relate that it is highly effective in 88% of uveitic cases with acceptable mild side effects. In our study, the adalimumab subgroup was the least effective BRM employed. Inflammation was decreased in 50% of eyes and was stabilized in a further 30%. Only two of 10 eyes demonstrated a worsening in inflammation.

In relation to daclizumab therapy, our study demonstrated that overall three patients improved on therapy and the other two patients remained stable. Only one of 10 eyes demonstrated a worsening in inflammation. As this group represents a heterogeneous group of disease entities this represents an excellent treatment response. The safety and efficacy of daclizumab in adult uveitis has already been reported[20] and the only pediatric experience documented was from our group. These cases demonstrated an improvement in inflammation in 50% of cases with no adverse effects recorded.

Our results coupled with the reports previously published in the literature suggest that BRM may be safe to use in children and are effective as adjunctive treatment in recalcitrant uveitis. Other issues that need to be considered when initiating therapy are the high cost of these agents and the difficulty in achieving approval from insurance companies for off-label use. The frequent dosing also raises compliance issues. This emphasises the need for a double-masked, placebo-controlled, randomized clinical trial to evaluate further the efficacy and safety of biological agents in childhood uveitis.

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