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Etanercept in Methotrexate-Resistant JIA-Related Uveitis

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ABSTRACT

We report our results with systemic Etanercept in patients with juvenile idiopathic arthritis in a joint ophthalmology–rheumatology clinic at a tertiary hospital. *Methods:* Patients with JIA on Etanercept were identified from a dedicated uveitis database. A retrospective review of electronic and paper-based patient records was performed. *Results:* Nine patients with JIA and current or previous treatment with Etanercept were identified, including six females and three males. Five patients with previous or current uveitis were noted. A further four were under observation for uveitis and required Etanercept for their joint disease. All nine patients had previously been taking Methotrexate, which had a suboptimal response in controlling arthritis or uveitis. Six out of nine patients did not show any uveitis activity at their last follow-up. Eyes of three patients still show signs of active inflammation in the anterior chamber (two on Etanercept and one off Etanercept). Severely impaired visual acuity (PL) was recorded in both eyes of one patient with long-standing persistent uveitis. Moderate visual loss in one eye of one patient was seen. The remaining seven patients did not show any significant loss of vision. Intraocular inflammation was not induced in any patient started on Etanercept. *Conclusion:* Etanercept may be useful in controlling JIA-related uveitis or arthritis in a pediatric patient when Methotrexate has had a suboptimal response in controlling the inflammatory activity.

Keywords: Anterior chamber, complications, Etanercept, eye, inflammation, juvenile idiopathic arthritis, Methotrexate, uveitis

INTRODUCTION

Juvenile idiopathic arthritis may cause significant ocular and joint inflammation, which may require systemic corticosteroids and Methotrexate. These drugs, used to treat the arthritis, are usually effective in controlling the ocular inflammation as well. Therapeutic dilemmas arise when uveitis does not settle with corticosteroids and Methotrexate. We report the use of Etanercept in a pediatric population requiring immune suppression due to active JIA-related inflammation.

METHODS AND MATERIALS

A retrospective review of electronic patient records at the Royal Liverpool Children's Hospital was performed. Data was prospectively collected and entered in a custom-built Liverpool pediatric uveitis database. Appropriate approvals were obtained. All research followed the tenets of the Declaration of Helsinki. Specific permission to use clinical data was obtained from patients or their guardians/parents. "Queries" were used to extract answers of specific questions from the clinical database. These were then correlated

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with paper-based patient records to improve reliability.

RESULTS

An electronic database review of 156 patient records showed nine patients with JIA with current or previous treatment with Etanercept. All patients were Caucasian. Average age of patients was 11 years (range of 6-16 years). Six females and three males were identified. Etanercept treatment had consisted of subcutaneous injection at a dosage of 0.4 mg/kg (maximum dosage 25 mg) twice a week.

Five patients with previous or current uveitis were noted. A further four were under observation for uveitis according to the joint BSPAR-RCO guidelines and required Etanercept for their joint disease. All nine patients had previously been taking Methotrexate, which had a suboptimal response in controlling arthritis or uveitis. Six out of nine patients did not show any uveitis activity at their last follow-up. Eyes of three patients still show signs of active inflammation in the anterior chamber (two patients on Etanercept and one patient off Etanercept).

Severely impaired visual acuity (PL) was recorded in both eyes of one patient with long-standing persistent uveitis. Another patient had significantly reduced vision in one eye (patient 8; Table 1). The remaining seven patients did not show any significant loss of vision (see Table 1).

DISCUSSION

Juvenile idiopathic arthritis (JIA) is the most common disease associated with childhood anterior uveitis.¹ This is usually treated with systemic steroids or methotrexate. Methotrexate (MTX) is an anti-metabolite and anti-folate drug. It acts by inhibiting the metabolism of folic acid. Most physicians regard Methotrexate to be relatively safe and effective in low doses. Routine twice-monthly hematological monitoring with a complete blood count, liver function tests, and creatinine is recommended. In our practice, Methotrexate is used orally, intramuscularly, or subcutaneously.

Methotrexate-resistant JIA may be treated with different immune-suppressing agents, depending upon the various patient factors and physician familiarity with drugs being used. Etanercept is a recombinant human TNFR p75-Fc fusion protein, which blocks TNF-alpha by competitive inhibition and prevents binding to the cell surface tumor necrosis factor receptor (TNFR).² Its use in treatment-resistant JIA-related uveitis is described in the literature.³

A review of published literature suggests a variable response to ocular inflammation with Etanercept.⁴ In

TABLE 1. Summary of patient status with Uveitis and their treatment with Etanercept.

ID	Age & sex	Previous uveitis	Current status of uveitis	Current/Previous use of Etanercept	Latest Snellen equivalent VA Right Left	Etanercept started	Active arthritis at last follow-up	ANA status	Comments
1	6/F	Yes	Under control	Current	6/6	June 2006	N	Positive	Methotrexate stopped
2	6/F	Yes	Under control	Current	6/6		Y	Negative	Concurrent Methotrexate
3	12/F	Yes	Active Uveitis	Current	6/6	Nov 2003		Positive	Intolerant to Methotrexate
4	15/F	No	No uveitis	Previous	6/5	Transient tm only		Unknown	Concurrent Methotrexate
5	15/M	Yes	Active uveitis	Previous	PL	Jan 2003	Y	Negative	Etanercept ineffective; HLA B27 + Currently Infliximab & Methotrexate
6	6/M	No	No uveitis	Current	6/6	Oct 2004	N	Negative	Concurrent Methotrexate
7	12/M	No	No uveitis	Current	6/5	April 2005	Y	Negative	Concurrent Methotrexate
8	16/F	Yes	Active uveitis	Current	6/12	Dec 2002	Y	Positive	Concurrent topical treatment. Etanercept 25 mg & oral prednisolone
9	11/F	No	No uveitis	Current	6/9	July 2006	Y	Negative	Concurrent prednisolone (tapering) and Methotrexate

our series, Etanercept was effective in reducing ocular inflammation in four patients with active uveitis. It was not effective in one patient and was changed to infliximab, which keeps the inflammation under control with only occasional relapses in this exceptional patient.

Adverse effects to Etanercept were not seen in any of our patients. Reported side-effects include neurological or psychiatric disorders, retro-bulbar optic neuropathy, weight gain, infection, cutaneous vasculitis with systemic symptoms, hemorrhagic diarrhea, uveitis flare, and pancytopenia.⁵

A recent study showed Etanercept and infliximab to be effective anti-TNF agents in the treatment of JIA-related uveitis. The same study also showed four patients developing uveitis for the first time while on Etanercept.⁶ This phenomenon was not observed in our patients. Whether or not this will develop remains to be seen in our series of patients on continuing follow-up. This includes four patients in our cohort on Etanercept (due to active JIA-related arthritis) who have not had uveitis before.

Most patients on subcutaneous Etanercept treatment can be treated at home, compared to other comparable immune modulators like Infliximab, which generally need intravenous infusion in a hospital setting. In our cohort, 90% of patients were managed by Etanercept subcutaneous injections at home with hospital follow-up visits for clinical assessments and blood monitoring only. The subcutaneous route is usually recommended due to better absorption, but in a pediatric setting the oral route may be used due to needle phobias in young children.

Our data suggests that Etanercept injected subcutaneously twice a week may improve the anterior chamber ocular inflammation in Methotrexate-resistant chronic uveitis in some children. "Etanercept induced uveitis" was not observed in

our patients. Further controlled studies with Etanercept are necessary to confirm its efficacy and safety in children based on longer-term follow-up.

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DECLARATION OF INTEREST

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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