CASE REPORT

Multi-modal Imaging in Etanercept-induced Uveitis: A Case Series

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Abstract:

Introduction:
To report with multi-modal imaging the clinical course of 3 patients with new-onset uveitis following treatment with etanercept.

Methods:
Retrospective case-note reviews were conducted of 3 patients previously established on etanercept who developed new-onset acute uveitis.

Results and Discussion:
Three patients were assessed with a mean age of 44.3 (43-47). Etanercept was indicated for the treatment of ankylosing spondylitis in two patients and psoriatic arthritis in 1 patient. Duration of etanercept treatment ranged from 7 to 10 years; however, in two cases, treatment recently changed to an etanercept biosimilar agent. Two patients were diagnosed with bilateral panuveitis and one patient had chronic relapsing anterior uveitis. Infection screen was negative in all three patients. 2 patients developed cystoid macular oedema as viewed on Spectral Domain OCT. Fundus fluorescein angiography was performed in one patient who demonstrated bilateral retinal vasculitis. All three patients were started on systemic and topical treatment. One patient received sub-tenon triamcinolone injection. Etanercept was discontinued for all patients. 1 of 3 patients lost vision at 7 months. 2 patients demonstrated long-term remission and one patient required intravitreal steroid implantation to stabilize an ongoing intraocular inflammation. Two patients who had complete remission were commenced on Adalimumab while the third patient was commenced on Secukinumab.

Conclusion:
The clinical course of uveitis developing paradoxically following etanercept treatment is variable. Multi-modal imaging is useful for the clinician that helps in diagnosing and monitoring associated macular oedema and retinal ischaemia. Cessation of etanercept and systemic corticosteroid treatment are often required to prevent ocular morbidity.

Keywords: Etanercept, Uveitis, Paradoxical adverse effects, Multi-modal imaging, Ocular inflammation, Ocular morbidity.

1. INTRODUCTION

Of the Anti-tumour Necrosis Factor (TNF) agents available for the treatment of rheumatological conditions, etanercept is most likely to be associated with the paradoxical instigation of uveitis in previously unaffected patients [1 - 3]. Early reports of this interesting phenomenon cited anecdotal evidence of the temporal relationship of resolution after drug discontinuation and positive rechallenge tests to implicate etanercept [4 - 6]. Large registry-based studies and systematic reviews argued not only that etanercept was less effective than other anti-TNF agents in reducing uveitis flares but also more likely to cause new-onset uveitis compared to other anti-TNF agents [3, 7-10].

The precise pathogenesis of these so-called Paradoxical Adverse Effects (PAE) is unclear, however, an imbalance in the cytokine milieu induced by TNF blockade has been hypothesized as the most likely mechanism. Other authors have suggested that TNF-alpha blockade increases susceptibility to infection from non-tuberculous Mycobacterium species and Propionibacterium acnes, which results in non-caseating granuloma formation [11]. Further, the differential immunological properties of the TNF-a soluble receptor of etanercept compared to the monoclonal antibodies have been postulated to explain the predilection of ocular inflammation in the former [12].
Table 1. Patient characteristics and demographic data.

| Patient | Age | Systemic Disease | Ocular Involvement | Interval of Etanercept Treatment to Onset of Uveitis | Corticosteroid Treatment | Modification to Biologic Treatment | VA on Presentation | Follow-up Duration (months) | VA at Last Follow up | Outcome |
|---------|-----|------------------|--------------------|---------------------------------------------------|-------------------------|-----------------------------------|-------------------|----------------------------|---------------------|----------|
| 1       | 43(F) | PA | Bilateral panuveitis + Macular oedema | - | Topical + pulsed IVMP + oral | Switched to Adalimumab | RE: 6/36 LE: 6/18 | 21 | 6/6 | Remission |
| 2       | 43(M) | AS | Bilateral panuveitis + retinal vasculitis | - | Topical + Oral | Switched to adalimumab | RE: 6/6 LE: 6/6 | 24 | 6/6 | Remission |
| 3       | 47(M) | AS | Left AAU + Macular oedema | - | Topical + subtenon + oral + intravitreal | Switched to Certolizumab pegol (ineffective); re-challenge of etanercept (exacerbation); switched to Secukinumab (incomplete remission) | LE: 6/6 | 7 | 6/12 | Partial remission requiring ongoing treatment |

F, Female; M, Male; PA, Psoriatic arthritis; AS, Ankylosing Spondylitis; AAU, Acute Anterior Uveitis; RE, Right Eye; LE, Left Eye; VA, Visual Acuity.

To date, the clinical parameters of patients with etanercept-induced uveitis have been elucidated only briefly in large retrospective studies or described in case reviews with limited imaging data. Our aim is to report the presentation, clinical course and management of 3 patients with etanercept-induced uveitis. We additionally evaluate the utility of multi-modal imaging techniques in the assessment, treatment and monitoring of these patients.

2. CASE REPORT

Three patients established on etanercept treatment who developed uveitis were identified (Table 1). All three patients denied previous episodes of uveitis.

2.1. Case 1

A 43-years-old Caucasian female was referred by her optician to the emergency department complaining of bilateral red and photophobic eyes for 1 week. She had a medical history of psoriatic arthritis and had been taking Etanercept (Enbrel, Pfizer, Brussels, Belgium) for 10 years. Her visual acuities were 6/36 in the right eye and 6/18 in the left eye (Snellen chart). Slit-lamp biomicroscopy was significant for injected conjunctivae and granulomatous “mutton fat” keratic precipitates were seen on the corneal endothelium. Anterior chamber (AC) cell activity was graded as 0.5+ in the right eye and 1+ in the left eye according to the SUN (standardisation of uveitis nomenclature) working group classification [13]. Her intraocular pressures were within normal limits and she did not have any evidence of intermediate or posterior uveitis.

She initially received treatment with intensive topical corticosteroids. At 1 week, her visual acuities remained unchanged with an increase in AC cell activity (2+ in the right eye and 1+ in the left eye). Optical Coherence Tomography (OCT) scans demonstrated gross macular oedema affecting both eyes (Fig. 1).

Fig. (1). OCT images of Case 1 at pre-treatment and at 3 months. Pre-treatment images show gross Cystoid Macula Oedema (CMO) in both eyes with intra-retinal cysts and subretinal fluid. Improvement is seen at 3 months, corresponding to an improvement in visual acuity.
Oral prednisolone was commenced at a dose of 30 mg/day. A baseline uveitis screening blood panel including serum ACE, blood-borne viruses, treponemal serology and T-spot with a chest x-ray was ordered to rule out infectious aetiologies and other pathologies, such as sarcoidosis, all were normal.

At 4 weeks, she reported no improvement in her vision and the macular oedema was persistent, necessitating 3 pulsed doses of intravenous methylprednisolone at a dose of 1 mg/kg followed by a tapering course of oral prednisolone. She was referred to the rheumatologist who had recommended discontinuing etanercept treatment.

Her vision improved over the next six weeks with quiescent eyes and resolution of macular oedema (Fig. 1). Her treatment has been changed to adalimumab at 3 months and she maintained good BCVA at 6/9 in the right eye and 6/6 in the left at 21 months of follow-up.

2.2. Case 2

A 43-years-old male with a background of Ankylosing Spondylitis (AS) treated with etanercept for 9 years presented to the Eye Casualty service with a one-week history of painful, red left eye with visual blurring. One month prior to his presentation, his rheumatologist switched his etanercept from Enbrel to a biosimilar agent Benepali (Samsung Bioepis, Delft, the Netherlands). His visual acuities were 6/6 in both eyes. Slit-lamp biomicroscopy of the left eye showed fine small keratic precipitates on the corneal endothelium and 2+ cells in the AC with 1+ flare. Intraocular pressures were within normal limits. Dilated fundal examination showed active vitritis with vitreous condensation (snowballs) in both eyes. He had bilateral but asymmetrical retinal peri-phlebitis with venous sheathing (Fig. 2).

A full uveitis blood screen including tuberculosis QuantiFERON, ANCA, ACE and treponemal serology was negative. An anterior chamber paracentesis was performed, which was negative for atypical cells, TB fungal or bacterial nucleic acid. Polymerase chain reaction testing of cytomegalovirus, Herpes simplex virus, varicella zoster virus was negative as well as serology for Bartonella, Borrelia and Treponema Pallidum. OCT showed no evidence of macula oedema. FFA confirmed the presence of active retinal vasculitis and leakage from retinal vessels in both eyes, with the left more florid than the right (Fig. 2).

He was treated with tapering oral prednisolone (starting at 40 mg OD for a week) along with topical corticosteroids and a recommendation was made to the rheumatologist to consider an alternative agent to etanercept. Vision remained at 6/6 in both eyes at 6 months (Fig. 2) but a repeat FFA showed improvement in the leakage around blood vessels. His rheumatologist switched his treatment to Adalimumab. At 24 months of follow-up, he had some very small areas of perivascular sheathing in both eyes with longstanding vitreous snowballs but maintained good vision at 6/6 in both eyes.

2.3. Case 3

A 47-years-old Caucasian male with a history of Ankylosing Spondylitis treated with etanercept for 7 years presented to the Eye Casualty department with a 1-week history of cloudy vision, pain, redness and photophobia in the left eye. Two months prior to his presentation, his rheumatologist switched his etanercept treatment from Enbrel to a biosimilar agent Erelzi (Sandoz, Kundl, Austria).

His Snellen visual acuity was 6/6 in both eyes on presentation. Biomicroscopy examination demonstrated small keratic precipitates in the left eye with 3+ of cells in the AC. He did not have any vitritis or posterior uveitis. Macula and optic disc appearances were normal.

His symptoms improved with a slow tapering course of topical corticosteroids and he was discharged at 7 weeks following complete resolution of the anterior uveitis. However,
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The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this paper.
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