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Title: **ADALIMUMAB IN REFRACTORY CYSTOID MACULAR EDEMA ASSOCIATED WITH BIRDSHOT CHORIORETINOPATHY**

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Concise title: Adalimumab in Birdshot macular edema

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ABSTRACT:

Purpose: To report the clinical outcomes of adalimumab therapy in cases of Birdshot chorioretinitis (BCR) with cystoid macular edema (CME) refractory to conventional immunotherapy. **Methods:** Retrospective case series of three BCR patients treated with adalimumab for refractory CME. The main outcome measure was central subfield thickness (CST) on optical coherence tomography. Any patients treated with local steroids and / or receiving systemic steroids higher than 40 mg prednisolone daily during adalimumab therapy were excluded. **Results:** At baseline, all patients were receiving systemic corticosteroids and two second-line immunosuppresive agents. The mean duration of treatment with adalimumab was 31.2 months (range: 17.2-52). The mean CST was 327 ± 112.7 μm (mean ± SD) at baseline and 256.2 ± 39.7 μm at 6 months and 235.5 ± 32.5 μm at 12 months. Adalimumab permitted cessation or reduction in the daily dose of oral prednisolone plus withdrawal of a second line agent in all patients. **Conclusions:** In these patients adalimumab was effective in the treatment of refractory CME.

KEYWORDS: Birdshot chorioretinopathy, Birdshot chorioretinitis, Adalimumab, Anti-tumour necrosis factor alpha (anti-TNF), Cystoid macular edema

INTRODUCTION

Birdshot chorioretinopathy (BCR) is a rare posterior uveitis involving the choroid and retinal vasculature that is strongly associated with the human leucocyte antigen HLA-A29.[1] It is an isolated ocular disorder characterized by the presence of multiple choroidal hypopigmented inflammatory lesions. The diagnosis remains clinical and the natural history is typically chronic resulting in a progressive decline in retinal function on visual field and electroretinogram testing.[2] Chronic cystoid macular edema (CME) is the predominant cause of central vision loss.[3-5] Early and aggressive immunosuppressive treatment is recommended to preserve vision,[6,7] with the standard of care being systemic corticosteroids plus conventional second line immunosuppresive drugs such as anti-proliferative agents and T cell inhibitors. In refractory cases biologic agents such as intravenous immunoglobulins, [8] daclizumab, [9] tocilizumab, [10] and infliximab [11] have all been tried with varying success.

The recent VISUAL trials have provided level 1 evidence supporting the clinical efficacy of adalimumab, a humanized monoclonal antibody targeted against tumor necrosis (TNF)-alpha, in reducing the frequency of inflammatory relapse for uveitis patients with a diverse range of uveitic diagnoses.[12,13] This included BCR, but a sub-group analysis was not reported and the inclusion criteria were not limited to refractory disease. Specific outcomes for BCR including electrodiagnostic tests (EDTs) were also not measured. In usual clinical practice, funding for high cost interventions such as adalimumab in rare conditions is often limited to patients who fail to achieve disease remission with the

standard of care, and in this context retrospective case series remain valuable in guiding treatment decisions. We are therefore reporting the clinical outcome of adalimumab therapy in cases of BCR with refractory CME.

METHODS

The medical records of all patients with CME associated with BCR treated with adalimumab in our center were reviewed. Any patients that received local steroid therapy (intravitreal or periocular) and/or systemic corticosteroid higher than prednisolone 40mg daily during adalimumab treatment were excluded. Data retrieved included age, gender, time since diagnosis and systemic immunosuppressive therapy at the start of adalimumab treatment. The best corrected visual acuity (BCVA), central subfoveal thickness (CST) determined by optical coherence tomography (OCT), and changes in immunosuppressive therapy regime were recorded for the duration of adalimumab therapy. The main outcome measure was the effect on CST. Wider retinal function was evaluated by analysis of serial EDTs performed before and during adalimumab treatment.

RESULTS

Three caucasian patients with bilateral BCR and CME refractory to conventional systemic immunosuppressive therapy were included in the study. All the patients were HLA-A29 positive. Two patients were female. The mean age at diagnosis of BCR was 49.9 ± 5.2 (mean ± SD) years (range: 46.6-55.9). The mean age at the time of starting adalimumab was 52.9 ± 6.1 (mean ± SD) years (range: 47.7-59.6), with a mean time from diagnosis to initiation of adalimumab of 3.0 ± 1.6 years (mean ± SD) (range: 1.2 - 4.1). Prior to adalimumab treatment, each patient received oral prednisone (all ≥10mg/day) and two second-line immunosuppressive agents (Table 1). None had previously received treatment with a biologic agent. All received adalimumab 40mg subcutaneously every 2 weeks with a mean duration of treatment of 31.2 months (range: 24.4-52). Table 1 summarizes the demographic data, systemic treatment and visual acuity at baseline and at the end of follow up.

1. OCT Central Subfoveal Thickness

Figure 1 shows the evolution of the CST for each patient from the start of immunosuppressive therapy to the end of follow up. Key therapeutic changes are highlighted. The mean CST for all patients (6 eyes) was 327 ± 112.7 μm (mean ± SD) at baseline and 256.2 ± 39.7 μm (mean ± SD) and 235.5 ± 32.5 μm (mean ± SD) after 6 and 12 months of adalimumab therapy (Fig. 2).

2. Visual Acuity

BCVA improved in 4 eyes (3 patients) and remained stable in 2 eyes (2 patients) from introduction of adalimumab to the end of follow-up. (Table 1)

3. Electrodiagnostic test (EDTs)

Serial ISCEV standard dark-adapted (DA) 3.0 (combined rod-cone) and light adapted (LA) 3.0 flicker (30Hz) ERGs were performed. Amplitudes of both A and B waves of the DA 3.0 response, 30 Hz flicker and latency of the 30 Hz flicker were analyzed over time and the average pre- and post-drug measurements were compared. There was an improvement in the amplitude of A and B waves of the DA 3.0 response in 4 of the 6 eyes post-treatment, an improvement in the amplitude of the 30 Hz flicker in 4 of the 6 eyes and an improvement in the latency in 5 of the 6 eyes post-treatment. Table 2 summarizes the results for each patient and each parameter pre- and post-treatment.

4. Changes to Systemic Treatment

At the end of follow up, adequate control of inflammation and CME permitted reduction of the systemic immunosuppressive therapy regimes in all 3 patients. Oral corticosteroid treatment was withdrawn in one patient and reduced in the other two patients to ≤7.5mg daily (Figure 1).

DISCUSSION

There is a strong and increasing evidence base in favour of anti-TNF alpha therapies for the treatment of uveitis, exemplified by the recent VISUAL trials.[12,13] However, a

dearth of disease specific data remains. For refractory BCR, a previous retrospective case series of patients treated with infliximab (a non-humanised, chimeric anti-TNF-alpha monoclonal antibody) concluded that this was effective in controlling disease in 89% of cases at 12 months.[11] This included a good response in 7 eyes in 5 patients with bilateral refractory BCR associated CME. Our results for adalimumab treatment endorse this observation, which suggests that rather than being drug specific effect, treatment benefit is attributable to the class of anti-TNF-alpha therapies as a whole. Furthermore, in all three cases, adalimumab led to an improvement in at least one electrodiagnostic parameter, a reduction in concomitant oral prednisone therapy and the number of second-line immunosuppressive treatments used. These limited data therefore support the use of adalimumab in rare cases of BCR with CME which is refractory to treatment with >10mg prednisone daily and 2 conventional second-line immunosuppressive agents.

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The authors do not have any proprietary interest in the materials described in this study.
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COMPLIANCE WITH ETHICAL STANDARDS

None of the authors have any proprietary interest in the materials described in this study. This report is limited to secondary use of information previously collected in the course of normal care (without an intention to use it for research at the time of collection) and therefore excluded from research ethics committee review.

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FIGURE LEYENDS

Fig 1 Diagram showing the central subfoveal thickness (CST), including the changes in systemic or ocular treatment, for each patient during the follow-up. There is an approximate interval of 6 months' time between vertical lines

Fig. 2 Mean central subfoveal thickness (CST) at the differences time intervals after treatment