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Therapeutic efficacy of intravitreal bevacizumab on posterior uveitis complicated by neovascularization

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Abstract

Purpose—To evaluate the therapeutic effect of intravitreal bevacizumab in patients with uveitis-associated choroidal/retinal neovascularization.

Methods—Two female patients (40 years, 15 years) with posterior uveitis, (one presumed ocular sarcoidosis, one lupus) were evaluated for neovascularization of the posterior segment. Both patients were given a single dose of 1.25 mg intravitreal bevacizumab.

Results—Significant anatomical and functional recovery was evident in both patients within a few weeks.

Conclusion—In selected uveitic patients, bevacizumab may be an option for managing neovascularization.

Keywords

anti-VEGF; bevacizumab; lupus retinopathy; neovascularization; proliferative retinopathy; sarcoidosis

Introduction

Uveitis is the cause of 30 000 new cases of blindness per year and up to 10% of all cases of blindness in the USA (Gritz & Wong 2004). Underlying systemic diseases such as sarcoidosis and systemic lupus erythematosus (lupus) (SLE) are often associated with uveitis. Sarcoidosis is a multi-systemic granulomatous disease characterized by non-caseating epithelioid granulomas that may affect virtually any organ system; in the eye, they frequently present as anterior, intermediate, posterior or pan-granulomatous uveitis. Similarly, lupus may cause non-granulomatous anterior or posterior uveitis, including retinal vasculitis defined as retinal vessel and vitreous inflammation. Neovascularization of the choroid and retina may arise in uveitic patients secondary to inflammation or ischaemia. We present two patients with significant neovascular disease who were managed unconventionally.

Patient 1

A 45-year-old Black female with pulmonary sarcoidosis (based on clinical and bronchoscopic evidence) was referred for decreased visual acuity (VA) of uncertain aetiology in the left eye. The cause was suspected to be presumed ocular histoplasmosis syndrome (POHS) or multifocal choroiditis (MFC). The vitals were stable and the patient was comfortable. VA was 20/20 in the right eye (OD) and hand motion in the left eye (OS). The anterior segment was unremarkable in both eyes (OU). The posterior segment was remarkable for bilateral multiple granulomatous chorioretinal lesions ranging from 300 to 400 μ m. There were vitreal cells (trace) bilaterally but the media was free of haze OU. The vessels were unremarkable bilaterally. The right macula did not display any cystoid macular oedema (CMO); the left macula was elevated with a prominent peripapillary neovascular complex (NV) that was evidently haemorrhaging and leaking subretinal fluid (Fig. 1A,B).

The clinical diagnosis was most compatible with ocular sarcoidosis. The differential diagnosis included ocular histoplasmosis, tuberculosis (TB) and syphilis. An anti-vascular endothelial growth factor (VEGF) agent – 0.05 ml of bevacizumab (1.25 mg) – was delivered intraocularly OD to address the vascular complex. On follow-up evaluation a week later, the patient tested negative by skin testing to TB, serologically to syphilis and by urine antigen to histoplasmosis.

The VA OS improved to 20/50 with coincident dramatic resolution in the subretinal fluid and decrease in the intraretinal haemorrhage associated with the NV (Fig. 1C,D) over a period of a week. The granulomatous lesions were unchanged clinically and on the angiogram (Fig. 1E,F). Oral prednisone was initiated at 0.5 mg/kg/day along with vitamin D and calcium supplements. The patient's VA OS continued to improve to 20/40 over 2 months. Oral prednisone was tapered and methotrexate introduced at 5 mg/week escalated to 15 mg/week with folic acid. After 3 months, the VA OS was stable off oral prednisone.

Patient 2

A 15-year-old Black female presented to the ocular immunology service at the National Eye Institute (NEI) with an existing diagnosis of SLE-associated retinal vasculitis and decreased vision, worse OD. Our patient met the acquired cellular resistance criteria for diagnosis of lupus, with a positive anti-nuclear antibody (ANA) titre, positive anti-dsDNA antibodies, positive anti-Smith antibodies, anaemia and leukopaenia, renal casts and facial discoid rash.

On her initial examination, the patient's VA was 20/200 OD and 20/63 OS. There was no afferent pupillary defect, and anterior segment examination was within normal limits in both eyes, other than trace cells OU. There were extensive intraretinal haemorrhages with evident retinal vasculitis throughout the posterior pole OU. There was 1 + haze OU, and the rest of the examination was unrevealing. Fluorescein angiogram (FA) revealed extensive choroidal and retinal ischaemia, pruned off retinal vasculature and retinal vasculitis in both eyes (Fig. 2A).

The patient was treated with systemic immunosuppression consisting of pulsed intravenous methylprednisolone, oral cyclophosphamide 100 mg daily (2 mg/kg/day) and oral prednisone 50 mg/day. Because of the significant retinal ischaemia observed on FA, the patient was also treated with panretinal photocoagulation (PRP) in both eyes.

After several months of therapy, the patient's VA recovered to 20/25 OU. However, she developed a frond of NV superotemporal to the right macula (Fig. 2B). At that time, she was maintained on systemic immunosuppression, and underwent multiple sessions of fill-in PRP in the autumn of 2005. Despite this therapy, vitreous haemorrhage developed in the right eye

in association with neovascularization elsewhere (NVE) 8 months after PRP with a decrease in vision to counting fingers. (Fig. 2C). The patient was then treated with one dose of 1.25 mg intravitreal bevacizumab. On re-evaluation a week later, the VA (OD) was 20/20, the NVE had regressed and the vitreous haemorrhage had almost cleared. The patient was evaluated 3 months after the intravitreal injection, with no recurrence of bleeding from the NVE and stable VA (Fig. 2D).

Comment

Our patient with ocular sarcoidosis demonstrated a dramatic therapeutic response to an anti-VEGF agent. Bevacizumab has been utilized as an affordable off-label medication for neovascular macular degeneration for 2 years with a good safety profile and short-term efficacy equivalence, as measured by VA, in anecdotal studies (Fung et al. 2006). A randomized controlled trial is underway comparing bevacizumab to the Food and Drug Administration (FDA)-approved ranibizumab in exudative macular degeneration. VEGF has been implicated in pulmonary sarcoidosis and systemic lupus; therefore, the ocular response to bevacizumab deserves some thought (Matsuda et al. 2004; Kuryliszyn-Moskal et al. 2007). Amongst varied factors involved in sarcoidosis, VEGF has been reported to be linked directly to prognosis in systemic sarcoidosis (Sekiya et al. 2003). This knowledge was the basis of attempting anti-VEGF therapy in patient 1.

Our lupus patient demonstrated retinal ischaemia, vasculitis and eventual vascular proliferation. Treatment options for this degree of disease include systemic immunosuppression and panretinal photocoagulation. Despite treatment with both of these modalities, our patient continued to progress to proliferative disease with vitreous haemorrhage. Vitreoretinal surgery was considered for this patient; however, the less invasive option of intravitreal bevacizumab was offered in preparation for any subsequent vitreoretinal procedures.

VEGF appeared to be a reasonable target (Takemura et al. 1992), and evidence of its efficacy was obvious in these cases. Bevacizumab may be a useful therapeutic option in selected uveitic patients in the management of NV. It may be worthwhile to evaluate the role of an anti-VEGF agent on select therapy-resistant, systemic-disease-associated uveitides with a neovascular component, in an effort to address the vascular component of the pathology (Papaioannou et al. 2006). The risks versus benefits of augmenting systemic immunomodulatory therapy in uveitis with a predominantly locally acting invasively delivered drug must be a tempering factor.

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Fig. 1.
(A) Left fundus: neovascular complex (NV) with haemorrhage superior to optic nerve head.
(B) Significant subretinal fluid (vertical). (C) A week after intraocular bevacizumab injection: marked regression of the NV. (D) Decreased haemorrhage and subretinal fluid (vertical). (E), (F) Before and after bevacizumab injection.

Fig. 2. (A) Lupus retinopathy. (B) Proliferative retinopathy 8 months after panretinal photocoagulation. (C) Subhyaloid haemorrhage, received intravitreal bevacizumab. (D) Resolution of haemorrhage 3 months after injection.