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CASE SERIES

Five-year visual results of intravitreal bevacizumab in refractory inflammatory ocular neovascularization

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Purpose: To assess the 5-year visual outcome of intravitreal bevacizumab in inflammatory ocular neovascularization.

Methods: Retrospective, multicenter, consecutive case series of eight patients with inflammatory ocular neovascularization refractory to standard therapy who were treated with intravitreal bevacizumab and followed for 5 years after first injection. The outcome measures included improvement of best-corrected visual acuity expressed as logarithm of minimum angle of resolution.

Results: Mean best-corrected visual acuity significantly improved from 0.58 at baseline (6/23 or 20/76; standard deviation = 0.32) to 0.20 at final assessment (6/10 or 20/32; standard deviation = 0.25) (n = 8; $P = 0.02$), a gain of 3.8 lines (median: three injections; eight eyes; eight patients). No ocular or systemic complications from intravitreal bevacizumab were noted.

Conclusion: At 5 years, intravitreal bevacizumab sustained significant visual improvement in ocular neovascularization due to a variety of inflammatory ocular diseases without major complications after a median of three injections.

Keywords: bevacizumab, choroidal neovascularization, punctate inner choroidopathy, toxoplasmosis, uveitis, Vogt–Koyanagi–Harada syndrome

Introduction

Uveitis-associated choroidal new vessel membranes (ie, choroidal neovascularization [CNV]) are relatively rare complications of posterior segment inflammation,[1–10] which mainly occur in multifocal choroiditis with panuveitis (39%), punctate inner choroidopathy (29%), serpiginous choroiditis (18%), and Vogt–Koyanagi–Harada (10%).[1–24] The current standard of care involves control of uveitis in a stepladder fashion with oral, periocular, or intraocular corticosteroids, along with immunosuppressive therapies.[11,12] When this medical therapy fails to cause CNV regression, additional interventions have been advocated, eg, argon laser photocoagulation, photodynamic therapy, and antivascular endothelial growth factor (anti-VEGF) drugs.[1–24] The authors' study group has reported short-term (3 months), mid-term (6 months to 2 years), and 3-year results of intravitreal bevacizumab in inflammatory CNV, showing significant visual improvement and regression of ocular neovascularization in a wide variety of ocular diseases.[10–12] The majority of studies analyzing the clinical efficacy of VEGF antagonists in uveitis or age-related macular degeneration or myopic CNV are short term (2 years or less).[1–24] In the current study, the 5-year visual and anatomic outcomes of intravitreal bevacizumab in inflammatory neovascular disorders in a multicenter, retrospective, consecutive, nonrandomized, interventional study are analyzed.

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Methods

Eight consecutive cases of recalcitrant (failed standard therapy)[11,12] inflammatory ocular neovascularization were treated with intravitreal bevacizumab and followed for 5 years ending March 2012. Intravitreal bevacizumab was injected using a 30-gauge needle in a sterile manner after topical anesthesia and povidone instillation in the lower cul-de-sac. The dosage of intravitreal injections varied initially between institutions, but the smaller dosage became uniform across the institutions later in the study. Injections were done according to monthly follow-up based on optical coherence tomography (OCT) and fluorescein angiography (FA). Patients were treated in a stepwise fashion with high doses of oral corticosteroid, with or without intraocular or periocular corticosteroid or immunosuppressive therapy as monitored by a rheumatologist. All patients signed an informed consent after being given information about the off-label usage of the drug.

Best-corrected visual acuity (BCVA) was assessed using either an Early Treatment Diabetic Retinopathy Study chart or Snellen chart and listed as logarithm of the minimal angle of resolution equivalents. Retreatment was done when there was recurrent activity evaluated by fundus examination, FA (leakage, growth of CNV), or OCT. Differences between final and initial BCVA were compared using paired Student's *t*-test, and a *P* value less than 0.05 was considered significant. CNV size was determined by the early stages of FA (in disc diameters).

Results

Eight consecutive eyes of eight patients – one male and seven females, five Caucasians and three Asians, mean age 33 years (range 17–51 years) – were examined at baseline and followed up for 60 months (Table 1). The right eye was involved in four subjects and the left in four subjects. Uveitis was active in two eyes at the time of ocular neovascularization. Prior therapies to intravitreal bevacizumab included: oral corticosteroid (five eyes), subtenon corticosteroid (two eyes), intraocular corticosteroid (two eyes), and immunosuppressive agents (two patients). Additional multiroute corticosteroid therapies were administered with reactivation of the disease prior to intravitreal bevacizumab throughout the 5-year study period. In most cases, immunosuppression was maintained 6 months after both the primary disease and CNV became inactive clinically, or by FA and OCT. Immunosuppression consisted of mycophenolate mofetil, methotrexate, and azathioprine. The diagnosis was punctate inner choroidopathy (three eyes), Vogt–Koyanagi–Harada disease (two eyes), ocular toxoplasmosis (two eyes), and tuberculosis (one case).

Mean CNV size was 1.4 disc diameters (range 0.5–2 disc diameters). CNV was subfoveal in three eyes, juxtafoveal in five eyes, and peripapillary in two eyes. Mean BCVA improved from 0.58 at baseline (6/23 or 20/76; standard deviation = 0.32) to 0.20 at final assessment (6/10 or 20/32; standard deviation = 0.25) (n = 8; $P = 0.02$ using two-tailed two-sample unequal variance *t*-test), a gain of 3.8 lines. BCVA improved by one to three lines in three eyes,

Table 1 Five-year follow-up of intravitreal bevacizumab (Avastin®) for inflammatory choroidal neovascularization

Number/ age (years)/ gender/race	Disease	Duration at initial injection of Avastin (months)	OD1/ OS2	Initial vision as logMAR	Final vision as logMAR	Prior PO steroid therapy (0 = no, 1 = yes)	Prior subtenon steroid therapy	Prior intraocular steroid therapy (0 = no, 1 = injection, 2 = dexamethasone intravitreal implant)
1/26/F/C	TX	0.5	2	0.7	0.4	0	0	0
2/30/M/A	TX	24	2	0.48	0.3	1	0	0
3/44/F/A	TB	1	1	0.3	0	1	0	0
4/51/F/C	PIC	2	2	0.7	0.7	0	0	0
5/30/F/A	PIC	1	1	0.9	0.1	0	0	0
6/40/F/C	PIC	4	1	0.0	0.0	1	0	1
7/29/F/C	VKH	12	1	1	0	1	1	2
8/17/F/C	VKH	96	1	0.54	0.1	1	1	0

more than three lines in three eyes, and was stable in two eyes. There was a median of three injections (mean of five injections; range of one to 15 injections) during the study period. The OCT machines changed during the study in the same center and were different between centers, which precluded the investigators from analyzing the change in central foveal thickness after therapy (Table 1). No injection-related complications were recorded, and the posterior capsular cataract in two eyes was mild, did not require surgery, and resulted from either uveitis or corticosteroid intake.

Discussion

The natural history of subfoveal CNV in inflammatory ocular neovascularization is generally poor.[25,26] Long-term results of photodynamic therapy in inflammatory ocular neovascularization appear to play a role in stabilizing vision.[11] Intravitreal injections of VEGF inhibitors represent a specific treatment influencing the pathogenic pathway of CNV and retinal neovascularization.[27–31] Excised inflammatory CNV overexpressed VEGF by immunohistochemistry,[27,28,31] hence the importance of enhanced VEGF expression in the pathogenesis of inflammatory ocular neovascularization. Furthermore, blockage of VEGF has not been shown to have an antiinflammatory effect.[32] Thus, treatment of the underlying inflammatory disease should play a central role in the management of uveitic CNV with the treatment regimen focusing on disease quiescence through the use of corticosteroids and immunosuppressive agents, while treating nonresponsive CNV with intravitreal anti-VEGF agents.[32]

Various large series of inflammatory neovascularization cases treated with VEGF antagonists have been published in the literature. Menezo et al noted visual stabilization or improvement in nine of ten patients with punctate inner choroidopathy treated with a mean of 1.9 injections of ranibizumab during an average follow-up of 1 year.[21] Adan et al described nine patients with various inflammatory CNV treated with bevacizumab injections.[13] CNV resolved in all affected eyes with BCVA improving in 88.8% of eyes with mean follow-up of 7.1 months, and after a mean of 1.3 injections. Tran et al described ten patients with uveitic CNV followed for a mean of 7.5 months.[9] CNV was subfoveal in eight cases and juxtafoveal in two cases. After a mean number of 2.5 injections, logarithm of the minimal angle of resolution BCVA improved significantly from 0.62 (20/55) to 0.45 (20/40) at 1 month, then remained stable during the follow-up. Lott et al treated 21 eyes with inflammatory ocular neovascularization and followed six eyes for 1 year with nonsignificant visual improvement from a median of 20/80 (21 eyes) to 20/60 (six eyes).[20] Kramer et al treated ten patients with inflammatory ocular neovascularization with prompt intravitreal bevacizumab as the first-line therapy and found that in a majority of patients a single injection led to CNV resolution with long-term visual improvement.[18]

The current series has the longest follow-up of bevacizumab in ocular use and attests to the sustained

Prior immunosuppressive therapy	Number of bevacizumab injections	Location of CNV membrane	Size of CNV (DD)	Uveitis at time of CNV (0 = inactive, 1 = active)	Initial foveal thickness (μ)	Final foveal thickness (μ)	Avastin dose (mL)	Complications
0	1	Subfoveal	1.5	0	NA	170	0.05	No
0	1	Subfoveal	1.5	0	389	278	0.05	No
0	3	Juxtafoveal	1.5	0	282	140	0.05	PSC
0	3	Juxtafoveal	NA	0	NA	NA	0.1 then 0.05	No
0	3	Subfoveal	0.5	0	NA	NA	0.05	No
0	13	Juxtafoveal	1	0	230	196	0.1 then 0.05	No
1	15	Juxtafoveal + peripapillary	2	1	244	202#	0.1 then 0.05	No
1	1	Juxtafoveal + peripapillary	2	1	142* (NA)	218** (NA)	0.1	PSC

Notes: *Just after injection; **during an episode of uveitis; #different machines used at follow-up.

Abbreviations: A, Asian; C, Caucasian; CNV, choroidal neovascularization; DD, disc diameter; F, female; logMAR, logarithm of the minimum angle of resolution; M, male; NA, not assessable because of difference in optical coherence tomography machines between exams and/or value not available on the exact dates of initial treatment and 5 years after the first injection; OD, right eye; OS, left eye; PIC, punctate inner choroidopathy; PO, per os; PSC, posterior subcapsular cataract; TB, tuberculosis; TX, toxoplasmosis; VKH, Vogt–Koyanagi–Harada syndrome.

positive effect of intravitreal bevacizumab on visual function in inflammatory ocular neovascularization. The drawbacks of the current study include the small size, the retrospective nature, and absence of a standard protocol for follow-up and treatment. A possible drawback is the conversion from Snellen to logarithm of the minimal angle of resolution. However, according to Kaiser, for patients with good visual acuity (>20/50), the difference between the Snellen and Early Treatment Diabetic Retinopathy Study charts was less than one line, with similar results for intermediate vision.[33] A large discrepancy existed for poor-vision eyes, which did not occur in the current study population. Nonetheless, the current study provides good evidence that intravitreal bevacizumab is an effective and safe therapy in the treatment of inflammatory CNV.

Disclosures

The authors report no conflicts of interest in this work. Institutional Review Board approval of the research was obtained from the American University of Beirut. The study was registered in the National Clinical Trials (NCT00645697).

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