Case Report

The Effect of Topical Bromfenac on Intraretinal and Subretinal Fluid in Neovascular Age-Related Macular Degeneration

Solmaz Abdolrahimzadeh[1], Valeria Fameli[2], Federico Di Tizio[1], Federico Di Staso[1], Vito Fenicia[1], Gianluca Scuderi[1]

[1]Ophthalmology Unit, Neurosciences, Mental Health and Sensory Organs Department, St. Andrea Hospital, Sapienza University of Rome, Rome, Italy, [2]Ophthalmology Unit, Department of Sense Organs, Sapienza University of Rome, Rome, Italy

Abstract

Purpose: To report the effect of topical bromfenac, a non-steroidal anti-inflammatory drug (NSAID), in a case of neovascular age-related macular degeneration (AMD).

Methods: An 85-year-old woman presented with a complaint of visual acuity reduction in the right eye. Comprehensive ophthalmological examination and retinal imaging were performed.

Results: Best corrected visual acuity was 2/100. Fundus examination showed reticular pseudodrusen and a small hemorrhage in the fovea. Fluorescein angiography showed an active neovascular membrane. Spectral-domain optical coherence tomography (SD-OCT) confirmed diagnosis and revealed subretinal and intraretinal fluid. The patient refused recommended intravitreal anti-vascular endothelial growth factor treatment and received topical bromfenac 0.09% twice daily. Follow-up with SD-OCT showed subretinal followed by intraretinal fluid reduction at 16 weeks after treatment.

Conclusion: Short-term reduction of subretinal and intraretinal fluid was observed with topical bromfenac monotherapy in neovascular AMD.

Keywords: Age-related macular degeneration, Bromfenac, Intraretinal fluid, Spectral domain optical coherence tomography, Subretinal fluid

Address for correspondence: Solmaz Abdolrahimzadeh, Ophthalmology Unit, Neurosciences, Mental Health and Sensory Organs Department, St. Andrea Hospital, Sapienza University of Rome, Via Di Grottarossa 1035-1039, Rome 00189, Italy.
E-mail: solmaz.abdolrahimzadeh@uniroma1.it
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Introduction

Neovascular age-related macular degeneration (AMD) characterized by choroidal neovascularization and exudation is the major cause of visual impairment and blindness in patients above 60 years of age.[1] The advent of intravitreal anti-vascular endothelial growth factor (anti-VEGF) therapy has been a major break-through in the treatment of neovascular AMD, and numerous clinical trials have shown that intravitreal anti-VEGF administration prevents vision loss and can improve visual acuity in patients.[2,3]

Steroids and non-steroidal anti-inflammatory drugs (NSAIDs) have been successfully employed in inflammatory conditions of the retina including cystoid macular edema.[4,5] Inflammation is among the complex multi-factorial mechanisms in the pathogenesis of neovascular AMD,[6] and this has led to the rationale that adjunctive agents such as steroids and NSAID can reduce retinal edema in this condition.[7,8] Since AMD is a life-long disease, some clinical trials have evaluated the effects of topical NSAID in combination with intravitreal anti-VEGF therapy to evaluate the additive effects on visual acuity improvement, central macular thickness reduction, and increase in intervals between anti-VEGF injections.[9-12]

The only report in the literature of monotherapy with NSAID in neovascular AMD is with topical nepafenac where the authors

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found improvement of vision, intraretinal fluid resolution, and only minor fluid accumulation in the subretinal space.[13] In the present paper, we report on the reduction of subretinal and intraretinal fluid in a patient with neovascular AMD who refused treatment with intravitreal anti-VEGF and received topical bromfenac (Yellox®, Bausch and Lomb).

Case Report

An 85-year-old woman experienced visual reduction in the right eye (RE). The patient referred previous cataract extraction with phacoemulsification in the left eye (LE) but no surgical or medical treatment in the RE. Best corrected visual acuity (BCVA) in the RE was 2/100 from a value of 20/40, 5 months previously, and 20/20 in the LE. The anterior segment was unremarkable in the RE and pseudophakic in the LE. RE fundus examination showed reticular pseudodrusen with hypo-hyperpigmentation and a small foveal hemorrhage. Spectral-domain optical coherence tomography (SD-OCT) was performed with the Heidelberg Spectralis (Spectralis Family Acquisition Module, V 6.0.11.0 Heidelberg Engineering, Germany) to obtain near infrared images and cross-sectional macular scans with the raster 20° ×15° 19-line and the radial 6-line scan protocol centered on the fovea with 100 frames averaged for each scan. The diagnosis of neovascular AMD with subretinal and intraretinal fluid was made. Fluorescein angiography was carried out and showed an active neovascular membrane [Figure 1]. The patient had not received previous intravitreal anti-VEGF therapy and refused recommended intravitreal anti-VEGF injections due to preexisting cardiac pathology. Informed consent was obtained, and topical administration of bromfenac 0.09% drops twice daily was initiated.

Following 10 weeks of treatment, SD-OCT showed marked subretinal fluid reduction, but intraretinal fluid was still present. Following 16 weeks of treatment, there was also a notable decrease of intraretinal fluid. The patient discontinued therapy due to hospital admission for the preexisting cardiac pathology (cardiac failure and chronic atrial fibrillation). Seven weeks after bromfenac discontinuation, SD-OCT showed increase in intraretinal and subretinal fluid [Figure 2]. Visual acuity remained unchanged throughout.

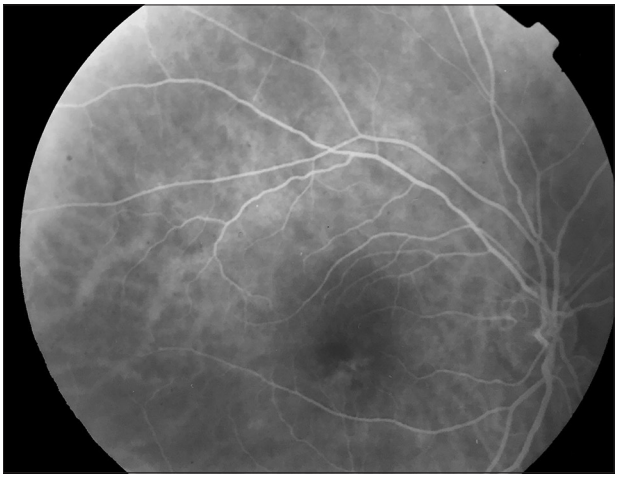

Figure 1: Fluorescein angiography image of the right eye showing neovascular age-related macular degeneration. Small area of blocked fluorescence caused by blood with adjacent hyperfluorescence due to leakage

Discussion

The clinical course of this case indicates that monotherapy with topical bromfenac was associated with reduction of subretinal fluid followed by reduction of intraretinal fluid in neovascular AMD.

Libondi and Jonas published the only reported case of monotherapy with topical NSAID, in a patient who refused anti-VEGF therapy. These authors reported visual acuity improvement, resolution of intraretinal fluid with minor fluid accumulation in the subretinal space using topical nepafenac alone.[13] In the present paper, we report our results with topical administration of bromfenac. Nepafenac and bromfenac are NSAIDs which block prostaglandin synthesis by primarily inhibiting cyclooxygenase 2, the enzyme that converts arachidonic acid to cyclic endoperoxides, which are precursors of prostaglandins.[14] Inflammation has been linked to the development of choroidal neovascular membranes.[6] In the animal model, Zhang *et al*. showed that the administration of a cyclooxygenase-2 selective antagonist attenuated choroidal neovascular lesions by reduction of macrophage infiltration, down regulation of VEGF in the retinal pigment epithelium-choroid complex, and reduced subretinal fibrosis by down regulation of tumor growth factor β_2.[14] Thus, based on the role of inflammation in the pathogenesis of neovascular membranes, some clinical trials investigated the use of intravitreal anti-VEGF therapy alone compared with intravitreal anti-VEGF associated with topical NSAID treatment in neovascular AMD. The parameters evaluated in these studies were mean macular thickness, BCVA, and injection intervals. However, the studies did not detail the qualitative changes of intra or subretinal fluid as observed with SD-OCT. Russo *et al*. compared patients undergoing intravitreal ranibizumab associated with topical ketorolac for 6 months to those receiving intravitreal ranibizumab alone and found that macular thickness reduction was greater in the combination treatment group while there was no effect on number of injections or BCVA improvement.[9] Semeraro *et al*. evaluated patients followed-up for 12 months receiving either intravitreal ranibizumab alone or in combination with topical ketorolac and found superior improvement in central retinal thickness and BCVA in the combination treatment group.[10] Intravitreal anti-VEGF associated with topical bromfenac was studied in two clinical trials.[11,12] Over 12 months of follow-up, Flaxel *et al*. studied intravitreal ranibizumab alone or in association with topical bromfenac and found superior improvement in central macular thickness in the combination treatment arm, whereas no differences in BCVA

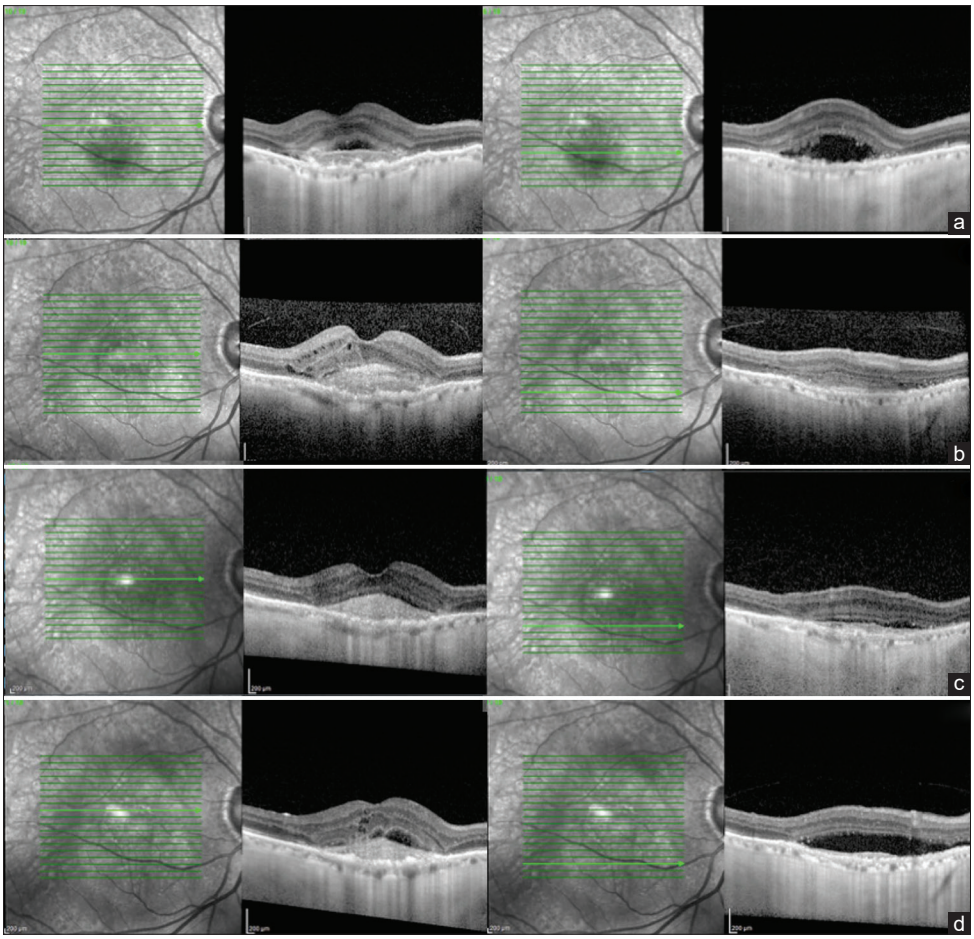

Figure 2: Spectral domain optical coherence tomography raster scans in the foveal area (left images) and in the peripheral macular area (right images) in exudative age-related macular degeneration during therapy and following discontinuation of topical bromfenac. (a) Prior to treatment initiation, foveal raster line shows a neovascular membrane with subretinal fluid and small hypo-reflective circular areas in the internal retinal layers indicative of intraretinal fluid. (b) Ten weeks of treatment, there is notable reduction of subretinal fluid but persistence of intraretinal fluid. (c) Sixteen weeks of treatment, there is notable reduction of intraretinal fluid and subretinal fluid. (d) Seven weeks following discontinuation of therapy, there is substantial increase in intraretinal and subretinal fluid

or number of injections were reported.[11] Gomi *et al*. found that a significantly lesser mean number of ranibizumab injections were required when anti-VEGF therapy was associated with topical bromfenac together with a tendency to superior retinal thickness reduction.[12] Interestingly, these authors chose patients with small areas of neovascularization with the rationale that larger lesions could be less responsive.[12] Therapeutic response may well vary with type, size, and specific characteristics of neovascular membranes. Indeed, there are paradoxical studies on the effect of NSAIDs on neovascular AMD. Zweifel *et al*. analyzed visual acuity, central point retinal thickness, and pigment epithelial detachment height in 21 patients who had persistent intraretinal or subretinal fluid despite an anti-VEGF loading dose. The authors added bromfenac bid to intravitreal therapy but did not find any beneficial effect.[15] Chen *et al*. studied the association of anti-VEGF therapy with nepafenac in neovascular AMD and did not report significant improvement of visual acuity or central foveal thickness, although they emphasized that all patients had recalcitrant AMD. Interestingly, they reported a reduction in cyst size or number of cysts and reduced subretinal fluid or pigment epithelial detachment when nepafenac was added to intravitreal therapy in 23 of the 25 patients they studied.[16]

The persistence of fluid negatively influences progression of neovascular AMD, and it has been advocated that a dry macula, based on OCT evidence of intraretinal and subretinal fluid, is the most desired result of intravitreal anti-VEGF treatment.[2,17] However, the interpretation of fluid localization in patients with neovascular AMD is still not completely clarified,[18] and a recent study reported that tolerance of some degree of subretinal fluid had similar results on visual acuity with respect to complete resolution of fluid following anti-VEGF treatment.[19]

The qualitative aspects of subretinal or intraretinal fluid have not been evaluated in previous clinical trials; thus, the dynamics of fluid reduction in the present case report may be of interest. It is clearly beyond the scope of this paper to draw conclusions on the efficacy of bromfenac on the types, size, and stages of neovascular AMD.[2,6,20] However, given

that we studied an uncommon case where recommended anti-VEGF therapy could not be administered, our report could solicit future investigations to evaluate the dynamics of macular edema in the management of neovascular AMD. This could provide further knowledge and possibly open-targeted therapeutic strategies for the relentless management of this lifelong pathology. Furthermore, while we clearly do not advocate monotherapy with NSAID as a substitute for anti-VEGF injections, the use of topical bromfenac can be considered in cases where anti-VEGF therapy is delayed in real-life situations.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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