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ORIGINAL RESEARCH

Use of nepafenac (Nevanac®) in combination with intravitreal anti-VEGF agents in the treatment of recalcitrant exudative macular degeneration requiring monthly injections

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Purpose: The purpose of this study is to determine the efficacy of combining topical nepafenac with monthly intravitreal injections of ranibizumab or bevacizumab in the treatment of recalcitrant exudative macular degeneration.

Methods: This was a retrospective, consecutive case series of patients with exudative macular degeneration requiring maintenance therapy of antivascular endothelial growth factor (anti-VEGF) injections at least every 6 weeks, who were started on topical nepafenac. Despite frequent anti-VEGF dosing, all patients included in the study had persistence of any combination of the following: intraretinal cysts, subretinal fluid, and/or pigment epithelial detachment. Patients underwent pinhole visual acuity, clinical exam, and optical coherence tomography (OCT) at baseline and every follow-up visit. Response to therapy was graded by reviewing quantitative and qualitative OCT data, and statistical analysis was done with paired Student's *t*-test.

Results: Twenty-five patients (average age 77; 14 male and 11 female) were reviewed; the mean number of previous injections was 17.4 (range 3–31). Baseline mean visual acuity was 20/55, and final mean visual acuity after 3 months of treatment was 20/51 ($P = 0.13$). Monthly mean central foveal thickness measurements were 248, 250, 257, and 247 μm ($P = 0.53$) at baseline, 1, 2, and 3 months, respectively. By the end of the 3-month time point, qualitative OCT findings on 13 patients treated with nepafenac were classified as stable, 10 as better, and 2 as worse.

Conclusions: There was no significant change in visual acuity or quantitative OCT measurements, but there appeared to be a mild trend toward improved anatomy and qualitative OCT findings when topical nepafenac was added to monthly anti-VEGF injections in patients with persistent intraretinal cysts, subretinal fluid, and/or pigment epithelial detachment. Further prospective studies with longer follow-up may be warranted.

Keywords: anti-VEGF, combination therapy, exudative macular degeneration, nonsteroidal anti-inflammatory, optical coherence tomography

Introduction

Age-related macular degeneration (AMD) is the leading cause of vision loss in the United States, and its prevalence is expected to increase by more than 50% by 2020.[1] The exudative form of AMD, defined by the growth of a choroidal neovascular membrane (CNVM) and a subsequent increase in vascular permeability, is present in 20% of patients and accounts for 90% of severe vision loss in patients with AMD.[2] Vascular endothelial growth factor (VEGF) plays a prominent role in exudative AMD and CNVM formation, and anti-VEGF therapies have become the standard of care

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for exudative AMD.[3–5] Despite monthly treatment, many patients continue to have persistent exudation.

Among the multiple factors implicated in neovascular AMD, inflammation is known to play an important role in CNVM formation.[6] A preliminary study of combination treatment with anti-VEGF therapy and a nonsteroidal anti-inflammatory drug (NSAID), topical bromfenac (0.09%) (Xibrom®; ISTA Pharmaceuticals Inc., Irvine, CA), reported a synergistic effect with both improved visual outcomes as well as a decreased need for intravitreal injections.[7] Nepafenac 0.1% (Nevanac®; Alcon Labs, Fort Worth, TX) is another topical NSAID used in the treatment of pain and inflammation associated with cataract surgery, as it has excellent corneal and scleral penetration.[8] Nepafenac inhibits both COX-1 and COX-2, reducing levels of prostaglandins and thromboxanes implicated in angiogenesis. We evaluated patients with recalcitrant exudative AMD treated with anti-VEGF therapy and topical nepafenac to determine the efficacy of combination therapy.

Methods

After obtaining approval of the study protocol by the Institutional Review Board of The Methodist Hospital in Houston, TX, USA, a retrospective, consecutive review of all patients seen at our practice between July 1, 2009, and December 31, 2009, was performed. We identified patients with exudative AMD who were prescribed off-label nepafenac three times daily in addition to anti-VEGF treatment with ranibizumab (Lucentis; Genentech, Inc., South San Francisco, CA) or bevacizumab (Avastin; Genentech, Inc.,). All patients included in the study had received at least three injections of intravitreal ranibizumab (0.5 mg/0.05 mL) or intravitreal bevacizumab (1.25 mg/0.05 mL) prior to this review and continued to require anti-VEGF therapy at least every 6 weeks for persistent exudation. For this study, persistent exudation was defined as any combination of the following: intraretinal cysts, subretinal fluid (SRF), and/or pigment epithelial detachment.[9]

Patients underwent pinhole visual acuity, clinical exam, and optical coherence tomography (OCT) at baseline and every follow-up visit, and main outcome measures studied were visual outcomes and response to therapy as graded by reviewing quantitative and qualitative time-domain OCT data (Stratus; Carl Zeiss Meditec, Inc., Dublin, CA). For the purposes of this study, retinal thickness in the central subfield was used for quantitative OCT measurements, while qualitative OCT grading was based on any change in either the number or size of intraretinal cysts, amount of SRF, and/or size of pigment epithelial detachment.

Pinhole Snellen visual acuities were converted to logarithm of the minimal angle of resolution for statistical analysis, and paired Student's *t*-test was used, with significance indicated by $P < 0.05$.

Results

Twenty-five patients (mean age 77; 14 male and 11 female) who completed 3 months of follow-up were identified; there were 10 right eyes and 15 left eyes involved in the review group (Table 1). The mean number of previous injections was 17.4 (range 3–31). Previous intravitreal agents included bevacizumab alone, 1 patient; ranibizumab alone, 21 patients; and both bevacizumab and ranibizumab, 3 patients. Mean visual acuity was 20/55 at baseline, and mean final visual acuity after 3 months of topical nepafenac three times daily in combination with monthly intravitreal anti-VEGF treatment was 20/51 ($P = 0.13$). Mean monthly central foveal thickness measurements from time-domain OCT were 248, 250, 257, and 247 μm at baseline, 1, 2, and 3 months, respectively, with no statistical difference between initial and final thickness measurements ($P = 0.53$). Compared to baseline, qualitative OCT findings on 13 patients treated with nepafenac were classified as stable, 10 as better, and 2 as worse at the 3-month time point.

Discussion

Although anti-VEGF agents have produced better results than ever seen before in the treatment of exudative AMD, most patients require repeated intravitreal injections at regular intervals to maintain the initial visual acuity gains, and a subset of patients have persistent fluid despite monthly maintenance treatment.[10,11] In addition to the significant burden both to the patient and society of frequent intravitreal anti-VEGF treatment, intravitreal injections also entail the rare but potential complications of pain, retinal tear or detachment, and endophthalmitis.[12]

As multiple pathways, including both angiogenesis and inflammation, have been implicated in the progression of exudative AMD, different combination therapies focusing on anti-VEGF agents plus verteporfin (Visudyne®; Novartis Ophthalmics, Bulach, Switzerland) photodynamic therapy with or without intravitreal steroids have been studied.[13] As photodynamic therapy carries a risk of sudden vision loss

Table 1 Demographics, characteristics, and findings of patients

Pt	Age	Sex	Eye	Prior Rx	VA (initial)	VA (final)	OCT_i, µm	OCT_f, µm	OCT findings	Change
1	70	M	OD	IVL X 11, IVA X 4	$20/30^{-2}$	$20/50^{-2}$	158	152	SRF	Same
2	68	M	OS	IVL X 3	20/25	$20/30^{-2}$	218	196	SRF	Better
3	74	F	OS	IVA X 8	$20/70^{-1}$	$20/80^{-1}$	251	232	IR cysts, PED	Same
4	89	M	OS	IVL X 31	$20/30^{-2}$	$20/30^{-1}$	222	227	SRF, PED	Same
5	70	F	OD	IVL X 26	$20/30^{+2}$	$20/25^{-2}$	221	227	SRF, PED	Better
6	78	M	OS	IVL X 19, IVA X 8	$20/50^{-1}$	20/40	241	235	SRF, IR cysts, PED	Same
7	75	F	OS	IVL X 12	$20/25^{-2}$	$20/25^{-2}$	229	274	SRF, PED	Same
8	71	F	OS	IVL X 28	$20/70^{-2}$	20/70	225	206	SRF, PED	Better
9	84	M	OD	IVL X 22	20/200	$20/200^{-1}$	282	311	IR cysts	Worse
10	73	M	OD	IVL X 17	20/30	$20/40^{-1}$	246	200	SRF	Better
11	76	F	OD	IVL X 20	$20/30^{+2}$	$20/25^{-2}$	178	165	SRF	Better
12	76	F	OD	IVL X 7	$20/40^{+2}$	$20/40^{-2}$	255	267	SRF, PED	Same
13	81	M	OD	IVL X 3	$20/60^{-2}$	$20/40^{-2}$	392	384	SRF, IR cysts, PED	Better
14	81	F	OS	IVL X 22	$20/40^{+1}$	$20/40^{-2}$	198	190	SRF, IR cysts, PED	Same
15	72	M	OD	IVL X 12	$20/60^{-2}$	$20/60^{-1}$	245	233	IR cysts	Better
16	81	M	OS	IVL X 3	$20/40^{-2}$	$20/30^{-2}$	260	262	SRF, IR cysts	Same
17	67	F	OS	IVL X 9	$20/30^{-1}$	$20/25^{-1}$	225	151	SRF, IR cysts	Better
18	73	F	OS	IVL X 30	20/80	20/60	352	271	SRF	Better
19	66	M	OS	IVL X 25	20/50	$20/40^{-1}$	254	308	SRF, IR cysts	Same
20	80	M	OS	IVL X 4, IVA X 9	20/200	20/200	173	193	SRF, PED	Better
21	88	F	OS	IVL X 20	20/200	$20/100^{+1}$	276	331	SRF, IR cysts	Worse
22	79	M	OS	IVL X 13	20/200	20/200	198	190	SRF, IR cysts	Same
23	74	M	OD	IVL X 17	20/200	20/200	548[1]	574[1]	IR cysts, PED	Same
24	94	F	OD	IVL X 23	$20/40^{-1}$	$20/30^{-1}$	179	140	IR cysts	Same
25	76	M	OS	IVL X 28	$20/30^{-1}$	$20/30^{-2}$	186	211	SRF	Same

Note: [1]OCT measurements taken from Heidelberg Spectralis (Spectralis; Heidelberg Engineering, Heidelberg, Germany).
Abbreviations: IVL, intravitreal ranibizumab; IVA, intravitreal bevacizumab; SRF, subretinal fluid; IR, intraretinal; OCT, optical coherence tomography; PED, pigment epithelial detachment; VA, visual acuity.

and choroidal hypoperfusion and intravitreal steroids can lead to cataract formation and elevated intraocular pressures, a topical anti-inflammatory medication may produce less side effects.

A nonrandomized, retrospective 6-month study by Grant suggested a synergistic effect for anti-VEGF treatment supplemented with topical bromfenac; patients in the combination arm had a statistically significant improvement in visual outcomes and a statistically significant decrease in the number of injections administered.[7] However, another study by Zweifel et al concluded that there was no objective or subjective benefit to topical bromfenac, and most patients discontinued the medicine after 2 months due to lack of perceived benefit.[14]

Nepafenac is a nonsteroidal anti-inflammatory prodrug approved for the treatment of postcataract surgery pain and inflammation. It has superior corneal penetration compared to other NSAIDs and is bioactivated by ocular tissues to amfenac.[8,15] Studies in rat models have indicated that it may play a role in inhibiting ocular neovascularization by inhibiting VEGF and retinal angiogenesis,[16,17] and a recent case report showed topical nepafenac produced regression of intraretinal and subretinal macular edema and a reduction of fluorescein leakage in exudative AMD.[18]

In this study, patients continued to receive anti-VEGF therapy that was supplemented with topical nepafenac three times daily; there were no safety issues or adverse events, and all 25 patients included in the review took nepafenac for 3 months. There was no significant change in mean visual acuity ($P = 0.13$) or quantitative OCT measurements ($P = 0.53$) of central foveal thickness from the initial visit to the final visit. Qualitative grading of OCT results did suggest there was some mild benefit. In most patients, dramatic differences in retinal anatomy were not seen on OCT scans; 23/25 demonstrated stable or improved anatomy, defined as fewer or smaller cysts or decreased amount or size of SRF/pigment epithelial detachment. The other two patients who were classified as worsening on qualitative OCT grading experienced an increase in intraretinal cysts, but patient 9 maintained vision, while patient 21 had a mild improvement in final visual acuity. In addition, during the course of the study period, patients 17 and 20 had complete but

only temporary resolution of SRF; neither of these patients experienced any change in visual acuity despite the interval changes seen on OCT.

As a retrospective study, there are many inherent limitations. There is a potential for selection bias as patients were not randomly selected for treatment; all had demonstrated lack of response to monthly injections, but there were differences in both the number of and the exact anti-VEGF agents previously administered. The lack of a control group and the small number of patients involved prevent us from accurately drawing conclusions about the efficacy of the treatment; although 25 patients finished 3 months of treatment, there were others that were started on the drops but discontinued due to lack of perceived effect and/or cost. There was a mild trend toward improved anatomic results based on qualitative OCT findings, although, even within the described limitations, we noted no visual benefit or significant improvement in quantitative OCT findings when adding topical nepafenac to patients receiving monthly anti-VEGF injections for exudative AMD. Future prospective studies with a control group and longer follow-up time may be warranted for further investigation.

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Disclosure

None of the authors have any proprietary interest in any of the data. Preliminary data from this study was presented at ARVO 2010.

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