

Bromfenac eyedrops in the treatment of diabetic macular edema: a pilot study

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ABSTRACT

Purpose: To evaluate the efficacy and safety of topical bromfenac in patients with newly diagnosed diabetic macular edema (DME).

Methods: In this pilot study including 17 patients with monocular, newly diagnosed DME, diagnosis of DME was established by the detection of retinal thickening at or within 500 μm of the center of the macula on ophthalmoscopic examination, according to the Early Treatment Diabetic Retinopathy Study classification. Central macular thickness (CMT) was determined by optical coherence tomography. Bromfenac sodium hydrate 0.9 mg/mL eyedrops were administered in the affected eye twice daily for 30 days. Primary endpoints were changes in best-corrected visual acuity (BCVA) and CMT at the end of therapy.

Results: Topical bromfenac significantly reduced mean CMT, from $465.41 \pm 118.47 \mu\text{m}$ at baseline to $388.88 \pm 152.63 \mu\text{m}$ posttreatment ($p = 0.02$). There was no significant change in BCVA and differences in mean macular volume fell just short of statistical significance ($p = 0.06$). Treatment was well-tolerated, and there were no topical or systemic side effects.

Conclusions: Topical bromfenac twice daily may play a role in the reduction of DME. These preliminary results warrant further larger multicenter studies to confirm our findings and establish whether topical bromfenac may be of long-term benefit in the treatment of DME.

Keywords: Central macular thickness, Diabetic macular edema, Pilot study, Topical bromfenac

Introduction

The global incidence of diabetes has continued to rise significantly over recent decades and the number of diabetic patients is estimated to increase from 382 million in 2013 to 592 million by 2035 (1). Diabetic retinopathy, the most common microvascular complication of diabetes, is the leading cause of blindness in adults in developed countries (2). Diabetic macular edema (DME), which may occur at any stage of diabetic retinopathy, results in loss of central vision and is the most common cause of permanent visual loss in patients with diabetes (2).

The initial pathologic changes in DME appear in the macular photoreceptors, Bruch membrane, retinal pigment epithelium,

and choriocapillaris. Disruption of the blood-retinal barrier with associated leakage of abnormal retinal vessels leading to swelling and thickening of the central area of the retina (the macula) is the main contributor to DME-related loss of visual acuity (VA) (3). Nowadays, the use of optical coherence tomography (OCT) is a straightforward procedure for quantifying macular retinal thickness, monitoring macular edema, and identifying vitreo-retinal traction in eyes with DME (4, 5).

While the etiology of DME is not fully understood, it is accepted that inflammation has a critical role in the development and progression of macular edema, suggesting a role for nonsteroidal anti-inflammatory drugs (NSAIDs) in the treatment of DME (3, 6, 7). Topical NSAIDs are commonly used in ophthalmology to stabilize pupillary dilation during intraocular surgery, control postoperative pain and inflammation, and treat allergic conjunctivitis and pseudophakic cystoid macular edema (6, 7). However, a growing body of evidence suggests that NSAIDs may also be beneficial in branch retinal vein occlusion (BRVO), diabetic retinopathy, ocular tumors, and age-related macular degeneration (AMD) (6-9).

Bromfenac (bromfenac sodium sesquihydrate; Yellox® 0.9 mg/mL, Croma Pharma GmbH, Korneuburg, Austria; and Bausch + Lomb, Inc., Rochester, NY) is a potent NSAID that provides targeted inhibition of the cyclooxygenase (COX-2) enzyme, thought to be the primary mediator of ocular inflammation (9). The lipophilicity of bromfenac provides enhanced penetration through the cornea and ocular tissues, rapidly

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producing physiologically active drug levels to reduce ocular inflammation (9). Currently, in the European Union, bromfenac ophthalmic solution administered twice daily is approved for the treatment of postoperative ocular inflammation following cataract extraction in adults (10). Bromfenac has been shown to be generally well-tolerated and effective against pain and inflammation in patients with ophthalmic disorders and in experimental animal models (9).

The aim of this study was to evaluate the effect of bromfenac eyedrops on newly diagnosed DME.

Methods

This was a pilot study, recruiting 17 consecutive newly diagnosed patients with monocular DME between April and October 2013. According to the Early Treatment of Diabetic Retinopathy Study classification, the diagnosis of macular edema was established by the detection of retinal thickening at or within 500 μm of the center of the macula on ophthalmoscopic examination (11). Patients who had previously received intravitreal injections of anti-vascular endothelial growth factor (VEGF) drugs and/or focal and grid photocoagulation for the treatment of DME were excluded.

Approval from the local ethics committee/institutional review board was obtained and the study was conducted in full accord with the tenets of the Declaration of Helsinki. Each participant received detailed information and provided written informed consent before inclusion.

All 17 patients underwent a full ophthalmic evaluation, including best-corrected VA (BCVA), slit-lamp examination, applanation tonometry, fundus biomicroscopy, and macu-

lar OCT scans (3D OCT-1000 Mark II; Topcon Co., Tokyo, Japan).

Eyedrops containing bromfenac sodium hydrate 0.9 mg/mL (Yellox[®]) were administered in the affected eye twice daily for 30 days. A full ophthalmic examination, as outlined above, was repeated at the end of the therapy course with topical bromfenac.

For each patient, glycated hemoglobin (HbA_{1c}) was measured before and after 30 days' therapy with topical bromfenac.

The primary clinical endpoints of this study were changes in BCVA and central macular thickness (CMT), which were evaluated initially and after 30 days of therapy. For analysis, BCVA was converted to the logarithm of the minimum angle of resolution (logMAR). Central macular thickness, which has been shown to be correlated with BCVA and severity of retinopathy (12), was determined by OCT. In addition, macular volume was also assessed.

Student *t* test for dependent means was used to evaluate changes in BCVA, CMT, and macular volume from baseline. A *p* value of ≤ 0.05 was considered statistically significant.

Results

This pilot study consisted of 11 (65%) men and 6 (35%) women; the mean age of patients was 63 ± 8.98 years (range 44-78). Eleven patients had type 2 diabetes and 6 had type 1 diabetes. The mean duration of diabetes was 15.1 ± 7.66 years (range 1-30) for the patients with type 2 diabetes and 34.5 ± 9.4 years (range 20-49) for those with type 1 diabetes. The demographic characteristics and medical histories of patients in the study are summarized in Table I. Each

TABLE I - Demographic characteristics and medical history of the study population

Patient	Sex	Age, y	Diabetes type (duration, y)	Pathology and prior treatment	CMT, μm		MV, mm^3		BCVA, logMAR	
					Baseline	Day 30	Baseline	Day 30	Baseline	Day 30
1	F	70	2 (16)	Severe NPDR (OU); CME (OS)	616	426	9.64	8.64	0.7	0.7
2	M	66	2 (12)	Severe NPDR with PRP (OU); CME (OS)	414	280	7.81	7.63	0.7	0.7
3	F	74	1 (33)	Moderate NPDR (OU); CME (OD)	526	442	9.45	9.46	0.5	0.5
4	M	63	2 (30)	Severe NPDR with PRP (OU); CME (OD)	601	223	11.37	7.64	0.8	0.7
5	F	47	1 (20)	Severe NPDR with PRP (OU); CME (OD)	350	352	8.07	8.09	0.4	0.4
6	M	52	2 (20)	Severe NPDR (OU); CME (OD)	489	387	7.95	7.89	0.5	0.4
7	M	67	2 (10)	Severe NPDR (OU); CME (OS)	481	601	12.28	13.21	0.4	0.4
8	M	63	2 (12)	Severe NPDR (OU); CME (OS)	288	181	10.43	10.4	0.2	0.3
9	M	64	2 (1)	Severe NPDR (OU); CME (OD)	409	227	8.62	6.74	0.8	0.8
10	M	62	1 (49)	Severe NPDR (OU) with PRP; CME (OS)	593	386	13.09	9.93	0.5	0.5
11	F	78	2 (24)	Severe NPDR (OU); CME (OD)	416	383	9.25	9.07	0.8	0.7
12	M	58	2 (15)	Severe NPDR (OU); CME (OS)	649	696	13.43	13.19	0.1	0.2
13	M	44	1 (35)	Severe NPDR with PRP (OU); CME (OD)	356	275	8.36	8.03	0.2	0.2
14	F	59	1 (38)	Severe NPDR (OU) with PRP; CME (OS)	442	525	9.84	10.24	0.3	0.4
15	M	69	1 (32)	Severe NPDR (OU); CME (OD)	318	321	10.46	10.4	0.6	0.6
16	F	70	2 (11)	Severe NPDR (OU); CME and pseudophakia (OD)	354	308	12.26	11.54	0.5	0.5
17	M	65	2 (15)	Severe NPDR (OU); CME (OD)	667	658	11.14	11.16	0.4	0.5

BCVA = best corrected visual acuity; CME = cystoid macular edema; CMT = central macular thickness; logMAR = logarithm of the minimum angle of resolution; MV = macular volume; NPDR = nonproliferative diabetic retinopathy; PRP = panretinal photocoagulation.



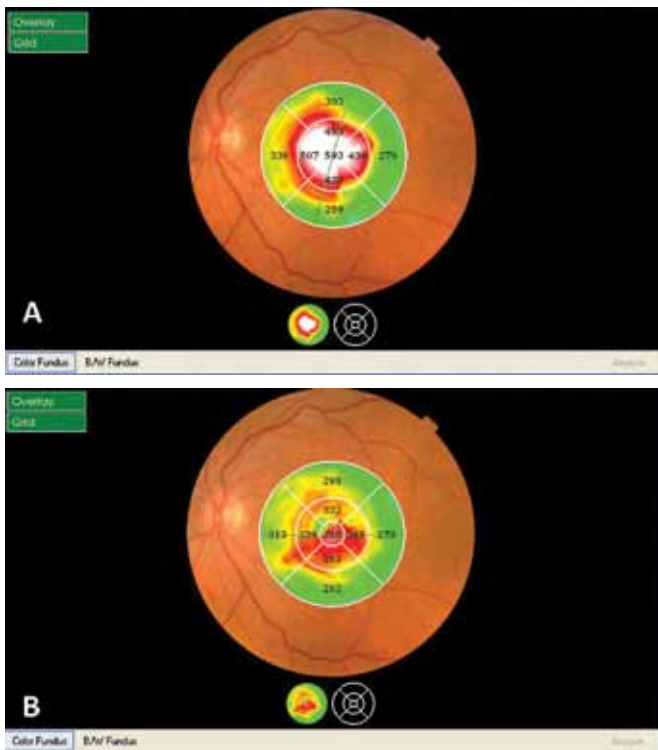


Fig. 1 - Spectral-domain optical coherence tomography (OCT) of the left macular area of a 62-year-old man with nonproliferative diabetic retinopathy in both eyes and cystoid macular edema in the left eye. (A) Before treatment. (B) After 30 days' treatment with topical bromfenac. The OCT maps were acquired in the same area before and after treatment.

individual patient showed almost identical values of HbA_{1c} before and after 30 days' therapy with topical bromfenac.

Administration of topical bromfenac did not significantly change VA. The mean pretreatment BCVA was 0.49 ± 0.22 logMAR and the final mean BCVA after 30 days of treatment was 0.5 ± 0.18 logMAR (not statistically significant; $p = 0.72$).

Bromfenac treatment significantly reduced mean CMT. The initial mean macular thickness was 465.41 ± 118.47 μm and the mean posttreatment macular thickness was 388.88 ± 152.63 μm , a statistically significant difference ($p = 0.02$). On the other hand, the initial and posttreatment mean macular volumes were 10.2 ± 1.82 and 9.6 ± 1.92 mm^3 , respectively, a difference that fell just short of statistical significance ($p = 0.06$).

Figure 1 shows pretreatment and posttreatment OCT images for a representative patient, a 62-year-old man with nonproliferative diabetic retinopathy in both eyes and cystoid macular edema in the left eye.

Treatment with bromfenac eyedrops was well-tolerated and no patient had topical or systemic side effects.

Discussion

Therapeutic approaches to treat and monitor DME have advanced considerably in recent years. Current treatment options for DME include focal/grid laser photocoagulation, intravitreal VEGF inhibitors, intravitreal steroids, combination

therapy with laser photocoagulation plus adjunct intravitreal steroid, intravitreal anti-VEGF drugs, and vitrectomy (5). Although laser photocoagulation became established as the gold standard therapy in the several decades after its introduction (5), there is accumulating evidence that anti-VEGF therapy (with or without laser photocoagulation) provides improved visual outcomes in patients with diabetic retinopathy and may be recognized as the current treatment of choice for DME (5). With regard to intravitreal steroids, owing to the risk of cataract formation and glaucoma development and their reduced ability to improve macular thickness, they play a secondary role in the therapy of DME, except for specific clinical situations (5).

A number of topical NSAIDs are formulated for ophthalmic use. These include bromfenac, diclofenac, flurbiprofen, ketorolac, and nepafenac. Increasingly, topical NSAIDs are being used in ophthalmology to reduce inflammation, treat postcataract surgery cystoid macular edema, reduce pain and photophobia after refractive surgery, and relieve allergic conjunctivitis-related itching (6, 7, 13). The approval of new topical NSAIDs, such as bromfenac, with enhanced drug penetration into the vitreous cavity has suggested new therapeutic opportunities, such as their use in AMD and DME (6, 7). The ophthalmologic utility of NSAIDs is based on the inhibition of COX enzymes and the consequent reduction in circulating prostaglandins, proinflammatory mediators responsible for inducing vasodilation, facilitating leukocyte migration, and stimulating pain, blood-ocular barrier disruption, and miosis.

The generally favorable tolerability profile of topical NSAIDs compared to topical steroids, which are associated with elevated intraocular pressure, retardation of wound healing, increased risk of corneal infection and perforation, and cataract formation (14), provides a therapeutic advantage and suggests an increasing role for topical NSAIDs in ophthalmology, alone or in combination with VEGF inhibitors.

Twice daily topical bromfenac has demonstrated efficacy in reducing postoperative pain and inflammation following cataract surgery in multiple clinical trials, and it was as effective as 4-time-daily diclofenac and ketorolac in acute pseudophakic cystoid macular edema, as reviewed by Jones and Francis (9). In patients with AMD, topical bromfenac has also been used as adjunctive therapy with intravitreal anti-VEGF therapy with ranibizumab or bevacizumab (15-17).

Clinical evidence suggests that bromfenac is effective in a range of ocular conditions, with favorable safety and tolerability. The twice-daily dosing schedule of bromfenac offers increased patient convenience, compared with other NSAIDs, and, together with good tolerability, may provide an attractive treatment option.

The results of our study suggest that bromfenac eyedrops may reduce macular thickness in patients with DME. In our patients with DME related to both type 1 and type 2 diabetes, there was a significant reduction in mean CMT of 76.53 μm after 30 days of treatment ($p = 0.02$). Decreases in CMT ≥ 50 μm are considered to be clinically relevant (15), and may be beneficial in sustaining visual function over the long term.

In eyes with DME, any change in the metabolic control of diabetes may have an influence on CMT. HbA_{1c} provides a good long-term measure of blood glucose control. In our study, each patient showed almost identical values of pretreatment

and posttreatment HbA_{1c}, a result implying that the reduction in mean CMT was not due to significant changes in average plasma glucose concentrations.

In this study, improvement in macular thickness was not associated with improvement in BCVA. This finding is not surprising; indeed, while the value of OCT as an evaluative tool in DME is unquestioned, other authors have shown that OCT measures of retinal thickness correlate poorly with VA (18). Furthermore, although a modest correlation between CMT and VA in patients with DME has been found in some studies (19-21), more recent research suggests that other mechanisms may influence visual function and the relationship between CMT and VA is complex and not yet fully understood (18).

Topical bromfenac was very well-tolerated by our patients. Systemic or local side effects were not observed. Our findings confirm the experience with bromfenac in other clinical studies, which have demonstrated a generally favorable tolerability profile. In a pooled analysis of data from 973 patients in the United States and Japan treated with topical bromfenac for postoperative inflammation following cataract surgery, one or more adverse events were observed in only 3.4% of the patients (10). The more common events comprised abnormal sensation in the eye (0.5%), mild to moderate corneal erosion (0.4%), local itching (0.4%), eye pain (0.3%), and redness (0.3%). Furthermore, no bromfenac-related systemic side effects were observed in 2 phase 3 clinical trials, and the overall incidence of adverse events was lower with bromfenac than placebo (22).

However, as with other NSAIDs administered topically (13), rare cases of corneal damage, consisting of corneal perforation and/or thinning and corneal melt, have been reported following the use of topical bromfenac (23, 24). In each of the 4 cases reported, bromfenac was used in patients with preexisting corneal compromise. Although serious corneal damage is very uncommon, bromfenac and other NSAIDs should be used only with caution in patients with corneal injury or disease, to minimize any risk of NSAID-related corneal toxicity.

To our knowledge, no previously reported study has addressed the use of topical bromfenac in the treatment of DME. As this was a pilot study, the patient numbers were small and sample size planning to ensure adequate power was not necessary. The most important limitation of the present study is that it was not a randomized prospective investigation in which the patients were randomly distributed between a study group and a control group. As monocular DME is a relatively infrequent condition, an alternative design could be to recruit patients with a bilateral condition and use the second eye as a control. This second, potentially more informative comparison will be the subject of further investigation. Although another important limitation is the relatively short investigation period (30 days), the finding that bromfenac reduced CMT is interesting, and may have clinical significance. In contrast, a recent controlled study in 125 patients with noncentral DME and good VA found that use of another topical NSAID, nepafenac 0.1% eyedrops, applied 3 times daily for 1 year did not have a significant effect on OCT-measured retinal thickness, compared with nepafenac vehicle (25). There were some indications of a potential reduction in retinal volume with nepafenac, but there was no

overall benefit on retinal thickening or in conversion to center-involved DME with topical nepafenac, and thus the effect of topical NSAIDs on DME remains unclear.

Given the current prominent role of intravitreal VEGF inhibitors in the treatment of DME, a recent study by Shimura and Yasuda (8) is of particular interest. They evaluated the effectiveness of topical bromfenac during treatment with intravitreal injections of bevacizumab in eyes with macular edema secondary to BRVO. These authors found that, although the combined use of bromfenac eyedrops and intravitreal bevacizumab did not affect the visual prognosis of BRVO-related macular edema, it had the advantage of reducing the number of bevacizumab injections. Likewise, in light of the results of our pilot study, it could be of value to assess whether or not topical bromfenac may also reduce the frequency of anti-VEGF injections in eyes with DME. This topic will be the subject of further investigation.

Conclusion

The results of this pilot study suggest that topical bromfenac twice daily may play a role in the reduction of DME. Further larger multicenter studies are necessary to establish whether or not topical bromfenac may be of long-term benefit in the treatment of DME.

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