https://doi.org/10.31288/oftalmolzh202421924

Use of bromfenac 0.09% (Broksinak) in the complex therapy for HLA-B27-associated anterior uveitis

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Background: *There is still no consensus among ophthalmologists as to whether the prolonged use of topical bromfenac 0.09% is feasible in therapy for acute uveitis.*

Purpose: *To improve the efficacy of treatment of HLA-B27-associated anterior uveitis through the use of Broksinak (containing bromfenac 0.09%) as an addditional therapy to the complex treatment regimen.*

Material and Methods: *This study involved 42 patients (72 eyes) with a diagnosis of HLA-B27-associated anterior uveitis. Follow-up duration was 24 months. All patients were administered systemic methylprednisolone and methotrexate. Patients of the bromfenac group were administered Broksinak eye drops (containing bromfenac 0.09%) as an additional treatment to primary systemic therapy over the course of the follow-up. Patients of the control group were administered dexamethasone 0.1% eye drops.*

Results: *There was no significant difference between the groups in terms of the number of recurrent uveitis episodes (p = 0.85) and laser flare reading during recurrent episodes (p = 0.56). In most recurrent uveitis episodes, laser flare readings were within the range of 20 to 50 ph/ms. There was a significant difference between the groups in the number of eyes that developed complications such as cataract (p = 0.05) and elevated intraocular pressure (p = 0.07). Cataract developed in 8 eyes of the bromfenac group and 19 eyes of the control group. At the final follow-up, elevated IOP was seen in 1 patient (1 eye) in the former group and 6 patients (7 eyes) in the latter group. At baseline, mean visual acuity (standard deviation (SD)) was 0.86 (0.21) for the bromfenac group and 0.78 (0.18) for the control group (p = 0.07). At the final follow-up, mean visual acuity (SD) was 0.86 (0.21) for the former group and 0.78 (0.18) for the latter group, ath the difference was significant (p = 0.006). No side effects from bromfenac 0.09% were noted in patients of the bromfenac group over the course of the study.*

Conclusion: *The use of Broksinak containing bromfenac 0.09% as an additional therapy to complex treatment regimens improves the efficacy of treatment of HLA-B27-associated anterior uveitis. With the prolonged use of Broksinak, the bromfenac group exhibited a reduction in recurrence severity not less than the group treated with dexamethasone eye drops 0.1%. Moreover, the side effects (cataract and elevated IOP) typical for dexamethasone were seen significantly less frequently, and no corneal lesions were detected in the former group.*

Keywords:

HLA-B27-associated anterior uveitis, uveitis, NSAIDs, corticosteroids, bromfenac, dexamethasone, cataract, glaucoma

Introduction

Uveitis as a category of ocular disease causes up to 5–10% of visual impairment globally. It is a major cause of visual morbidity with prolonged visual loss occurring in two-thirds of patients, and up to 22% meeting the criteria for legal blindness at some point during the course of the disease [1]. A T-cell mediated immune response to ocular autoantigens underlies the pathogenesis of autoimmune uveitis, which results in acute or normal dysregulation of ocular immune response [2]. Anterior uveitis is the predominant form of uveitis in most populations studied, accounting for approximately 50–60% of all cases of uveitis seen in tertiary referral centers. HLA-B27-associated acute anterior uveitis is the most important form of anterior uveitis (acute and chronic forms combined), accounting for 18-32% of all cases of anterior uveitis [3]. Management includes local (instillation or injection) and systemic glucocorticoids, immunosuppressants (e.g., Methotrexate), and tumor necrosis factor-α (TNF-α) inhibitors [4, 5].

All these medications, however, have rather severe side effects when used for long periods [6-9]. Complicated cataract and elevated intraocular pressure (IOP) are common complications associated with long-term use of glucocorticoids [10].

Much research is underway to develop novel medications and more effective treatment schemes with reduced side effects for patients with uveitis.

Our attention has been drawn by bromfenac ophthalmic solution (bromfenac) 0.09% as a potential candidate for long-term and regular treatment of uveitis due to its anti-inflammatory effects and low incidence of serious side effects [11].

The purpose of this study was to improve the efficacy of treatment of HLA-B27-associated anterior uveitis through the use of a medication containing bromfenac 0.09% as an additional therapy.

Material and Methods

This study was conducted at the Filatov Institute of Eye Diseases and Tissue Therapy and involved 42 patients (72 eyes) aged 18 to 45 years with a diagnosis of HLA-B27-associated anterior uveitis. Of these patients, 30 had bilateral uveitis and 12 had unilateral uveitis. An ophthalmic examination included assessment of patient complaints, visual acuity assessment, biomiscroscopy, ophthalmoscopy, tonometry, and laser flaremetry (Kowa FM-600 laser flare meter, Kowa Company Ltd., Nagoya, Japan). Follow-up duration was 24 months. This study included only patients who were administered systemic methylprednisolone (at a daily dose of 2 to 8 mg) and methotrexate (at a weekly dose of 7.5 to 17.5 mg). This study excluded patients who either did not receive the above medications, or were receiving other therapy (e.g., adalimumab, sulphasalasine, asatioprin, mycophenolate moferil, etc.) to avoid error in assessing the efficacy of additional bromfenac 0.09% therapy. Other inclusion criteria were patients having an onset of disease exacerbation and being already on systemic therapy. That is, at the beginning of the study, they had had a history of at least one episode of uveitis.

The first recurrence episode was treated with topical corticosteroids in the form of peribulbar and/or subconjunctival injection, systemic non-steroidal anti-inflammatory drugs (NSAIDs), and sometimes increased doses of methylprednisolone and/or methotrexate, under in-patient conditions at the beginning of the study. In addition, antihypertensive medications, duiretics and neuroprotectors were administered in the presence of cystoid macular edema or optic nerve edema.

Patients with elevated IOP, cataract, positive family history of glaucoma, and patients who were administered increased doses of systemic methylprednisolone and/or methotrexate were excluded from the study.

The amount of anterior chamber inflammation was measured by the laser flare meter, expressed as photons per millisecond (ph/ms), and categorized as category 1 (< 20 ph/ms), category 2 (20-50 ph/ms), category 3 (50-100 ph/ms), and category 4 (> 100 ph/ms).

Patients were divided into two groups. Patients of the bromfenac group (21 patients, including 14 patients with bilateral uveitis and 7 patients with unilateral uveitis) were administered Broksinak eye drops (containing bromfenac sodium sesquihydrate 0.09%) daily for a month as an additional treatment to primary systemic therapy for each recurrence event over the course of the study. Controls (21 patients, including 16 patients with bilateral uveitis and 5 patients with unilateral uveitis) were administered dexamethasone eye drops 0.1% daily for a month as an additional treatment to primary systemic therapy for each recurrence event over the course of the study. Over the first one or two weeks after the onset of the recurrent event, dexamethasone was administered 3 times a day in category 1 inflammation, 4 times a day in category 2 inflammation, 6 times a day in category 3 inflammation, and 8 times a day in category 4 inflammation. After event completion, dexamethasone was administered twice daily over 3 weeks.

Efficacy measures included annual rate of uveitis relapses, laser flare readings during the recurrent event, visual acuity at the onset of recurrent event and during the remission stage (one month after the onset of the recurrent event), recurrence duration, and development of complications (cataract and/or elevated IOP).

Statistical analyses were conducted using Statistica 9 (StatSoft, Tulsa, OK, USA) software. Data are presented as mean and standard deviations. Pearson correlation coefficients were calculated. The level of significance $p \leq 0.05$ was assumed.

The study followed the ethical standards stated in the Declaration of Helsinki, the European Convention on Human Rights and Biomedicine and relevant laws of Ukraine. Informed consent was obtained from all patients.

Results

Of the 42 patients included in the study, 31 had uveitis in the presence of seronegative spondyloarthropathy and 11 had isolated uveitis. Of the 31 patients with uveitis in the presence of seronegative spondyloarthropathy, 27 had ankylosing spondyloarthritis, and 4 had psoriasis. All these patients were followed both by their ophthalmologist and their rheumatologist.

In patients of the bromfenac group, the mean number of recurrent uveitis episodes over two years was 1.74 (SD, 1.12; range, 1 to 5); the total number of recurrent uveitis episodes in this group was 47.

In patients of the control group, the mean number of recurrent uveitis episodes over two years was 1.76 (SD, 1.08; range, 1 to 5), and the total number of recurrent uveitis episodes was 51.

There was no significant difference between the groups in terms of the number of recurrent uveitis episodes (p =

0.85) and laser flare reading during recurrent episodes (p = 0.56).

In the bromfenac group and the control group, category 1 inflammation (< 20 ph/ms) was found in 7 and 9 recurrent episodes, respectively, category 2 inflammation (20-50 ph/ms), in 29 and 30 recurrent episodes, respectively, category 3 inflammation (50-100 ph/ms), in 10 and 9 recurrent episodes, respectively, and category 4 inflammation (> 100 ph/ms), in 1 and 3 recurrent episodes, respectively.

At baseline, mean visual acuity (SD) was 0.86 (0.21) for the bromfenac group and 0.78 (0.18) for the control group (p = 0.07). At the final follow-up, visual acuity significantly improved (p = 0.006) to 0.92 (0.12) in the former group and to 0.65 (0.16) in the latter group.

Mean recurrence duration (SD) was 9.82 (1.96) for the bromfenac group and 10.15 (2.14) for the control group, but the difference was not significant. No side effects from Broksinak were noted in patients of the former group over the course of the study. By the final follow-up, cataract developed in 8 eyes of the bromfenac group (all these cataracts were mild) and 19 eyes of the control group (10 mild cataracts and 9 immature cataracts), with a significant difference (p = 0.005) between these groups in the percentage of eyes with cataract developed. In addition, at the final follow-up, elevated IOP was seen in 1 patient (1 eye) in the bromfenac group and 6 patients (7 eyes) in the control group, with a significant difference (p = 0.007) between these groups in the percentage of eyes with elevated IOP. Therefore, the number of uveitis complications (cataract and elevated IOP) was significantly smaller in the former group.

Discussion

The initial choice of treatment for uveitis is dependent on a number of factors, including the degree of inflammation, the laterality (unilateral versus bilateral), the anatomic location (anterior, intermediate or posterior uveitis), and the presence and extent of systemic disease. Other important factors to consider in treatment decisions would be the experiences and perspectives of patients and carers.

A study by Tallouzi and colleagues [12] identified different core domains which are important to patients with non-infectious posterior segment-involving uveitis, including visual function, treatment burden, treatment side effects and disease control. They developed a core outcome set (COM) for clinical trials in non-infectious posterior segment-involving involving uveitis. Because anterior non-infectious uveitis may be accompanied by posterior segment involvement (cystoid macular edema and/or optic nerve edema), and the diseases are almost similar with regard to pathogenesis, we believe it is reasonable to focus on the study [12] and use COM terms. In non-infectious uveitis, the therapy is aimed at suppressing the local immune response. It is often useful for the clinician to think of the concept of disease activity versus damage. Uncontrolled disease activity could potentially result in complications (e.g., optic atrophy and cystoid macular edema) leading to irreversible loss of vision. Local therapy for non-infectious uveitis is aimed at disease control and the reduction of complication risk.

Corticosteroid eye drops are still the first-line treatment option in anterior uveitis. Corticosteroids have an impact on almost the entire inflammatory cascade and suppress production of numerous inflammatory mediators, predominantly through inhibition of phospholipase A2 and cyclooxygenase-2. Corticosteroid eye drops are used predominantly in anterior uveitis. Dexamethasone and prednisolone acetate eye drops are the two most commonly used corticosteroid eye drops in the treatment of anterior uveitis, with the latter drug achieving higher concentrations in the aqueous humor of the anterior chamber. Only difluprednate achieves significant concentrations in the posterior segment and is considered effective in the treatment of cystoid macular edema; it, however, causes a significant increase in IOP. Fluorometholone and loterprednol do not cause a significant increase in IOP, but have a lesser impact on inflammation compared to difluprednate [10].

The treatment regimen of topical corticosteroids depends on disease activity levels and may range from one drop every hour to one drop every other day. Topical steroid eye drops are often prescribed as a course of hourly intensive treatment for a week, followed by a slow taper over the following weeks [13]. Cataract and glaucoma are classical side effects of topical corticosteroids.

Although there are several theories and the exact mechanism of how an elevation in IOP happens remains unclear, topical steroid eye drops are thought to increase aqueous outflow resistance by affecting the extracellular matrix of the trabecular meshwork [14]. In fact, following the use of topical dexamethasone, between 34% and 42% of individuals can develop an IOP rise from a baseline of 6 mmHg to 15 mmHg, to a final pressure of 20 mmHg to 31 mmHg [15].

Unfortunately, since many of the early generation topical steroid eye drops were introduced prior to modern regulatory requirements, placebo-controlled trials and comparative studies looking at their effects on IOP are limited [16].

Another well-known side effect of topical corticosteroids is the development of cataracts, particularly posterior subcapsular cataracts. However, non-infectious uveitis in itself is a risk factor for the development of cataracts, with the 5-year risk of developing cataracts being 3-times higher in patients with uveitis compared to controls [1].

In a pediatric cohort of patients with juvenile idiopathic arthritis (JIA), the prevalence of cataract was 44% (out of 140 children), affecting 77% of panuveitis patients, 48% of anterior uveitis patients, and 48% of intermediate uveitis patients. Other risk factors identified for the development of cataracts included the number of uveitis flares per year, the presence of cystoids macular edema,

and posterior synechiae. Remarkable, while the use of local corticosteroid injections is a risk factor, treatment with topical corticosteroids was not found a significant risk factor. This highlights the importance of an appropriate long-term regimen for patients with chronic uveitis who require long-term corticosteroids, to reduce the risk of cataract formation [17].

A retrospective review of JIA patients by Thorne and colleagues [18] over 4 years demonstrated that there were an 87% reduction in the risk of cataract formation in patients who were using topical steroid eye drops less than three times a day, compared to patients using these more than three times a day. This is an important consideration when counseling patients requiring long-term topical steroid eye drop therapy, as uncontrolled disease activity with frequent flares probably constitutes a greater risk of developing cataracts than simply as a side-effect of topical steroid eye drops.

The patients included in the current study had no cataract or elevated IOP at baseline. In addition, they had no family history of glaucoma. However, with the use of dexamethasone eye drops, some of them developed complications in the form of cataract and/or elevated IOP.

There was no significant difference between the bromfenac group and control group in the number, severity and duration of recurrent uveitis episodes.

Another class of the anti-inflammatory drugs used in the uveitis is the NSAIDs. In ophthalmic practice, topical NSAIDs are commonly used for the treatment of postoperative inflammation and macular edema following cataract surgery. Several types of topical NSAIDs have been approved by the US Foof and Drug Agency (FDA) for this purpose, including bromfenac 0.09%. NSAIDs exert their anti-inflammatory action by inhibiting the cyclooxygenase enzymes (COX1 and COX2), therefore inhibiting the conversion of arachidonic acid into inflammatory mediators such as prostaglandins and thromboxanes. Similar to glucocorticoids, the main route used for the application of NSAIDs in uveitis is topical administration.

Although the evidence of their efficacy is limited, topical NSAIDs are frequenly used off-label for the treatment of uveitic macular edema, as they are considered to be safe and effective alternatives in the topical management of ocular inflammation, due to the serious adverse effects associated with steroid use, as mentioned above [19].

There have been scattered reports of adverse events, including corneal melting and perforation, associated with topical NSAIDs [20]. It is a potential corneal abnormality (ranging from punctuate keratopathy to corneal perforation) that stll limits the long-term use of bromfenac in the treatment of uveitis [21, 22]. It is likely that this is associated with a prior history of corneal complications with the use of topical diclofenac sodium and evidence of the decrease in corneal sensitivity in normal corneas with the use of topical diclofenac sodium [23, 24].

Yanai and colleagues [25], however, reported that bromfenac sodium eye drops are safe with respect to corneal sensitivity and tear secretion in subjects with normal ocular surface condition.

Radwan and colleagues (2013) [26] evaluated the efficacy of bromfenac drops alone or with a single intracitreal injection of bevacizumab (IVB) or triancinolone acetonide (IVTA) in the treatment of uveitic macular edema (UME). They concluded that IVB and IVTA are both effective in improving visual acuity and decreasing central macular thickness (CMT) up to 3 months. In addition, bromfenac is inaffective alone for UME treatment, but may have a synergistic effect with IVTA in reducing CMT up to 3 months of follow-up.

Topical corticosteroids are also used to treat UME. In a retrospective case series of 58 patients (72 eyes) with non-infectious UME trated with topical 0.05% difluprednate, CMT decreased by an average of 17%. At 30 days, 76% of eyes had improved, with 48% of eyes achieving resolution of UME. However, due to the higher rate of complications from glaucoma and cataract, it has not yet been approved by European Medical Agency [1].

For cases of intermediate, posterior, or panuveitis, topical therapy alone is usually inadequate due to poor tissue penetration, although it remains crucial as additional therapy. The only exception to this is topical NSAIDs such as bromfenac, with evidence of therapeutic levels in the retina after topical application [6, 27, 28].

Therefore, the results of the current study add to what is known on topical application of bromfenac. In the current study, significantly more eyes developed cataract and elevated IOP (the typical complications associated with dexamethasone) in the dexamethasone group (19 eyes and 7 eyes, respectively) than in the bromfenac group (8 eyes and 1 eye, respectively), possibly, due to non-infectious uveitis proper. In addition, no corneal lesions were found in the latter group, and there was no significant difference between the groups in terms of the number, severity and duration of recurrent uveitis episodes.

Consequently, the use of Broksinak containing bromfenac 0.09% as an additional therapy allowed us to improve the efficacy of treatment of HLA-B27-associated anterior uveitis. With the prolonged use of Broksinak, the bromfenac group exhibited a reduction in recurrence severity not less than the group treated with dexamethasone eye drops 0.1%. In addition, the side effects (cataract development and elevated IOP) typical for dexamethasone were seen significantly less frequently, and no corneal lesions were detected in the former group.

With the prolonged use of Broksinak, the bromfenac group exhibited a reduction in recurrence severity not less than the group treated with dexamethasone eye drops 0.1%. Moreover, the complications (cataract and elevated IOP) typical for dexamethasone were seen significantly less frequently, and no corneal lesions were detected during the use of Broksinak.

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Disclosures

Received 02.12.2023

Accepted 30.03.2024

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Author Contributions: *OVZ: Conceptualization; Methodology; Data curation; Writing - original draft preparation; Writing – review & editing; Data analysis.*

Funding: *No funding was received for this article.*

Conflict of Interest: *The author state that there are no conflicts of interest that might influence their opinion on the subject matter or materials described or discussed in this manuscript.*