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ORIGINAL RESEARCH

Efficacy and Safety of Bromfenac for the Treatment of Corneal Ulcer Pain

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ABSTRACT

Purpose: To evaluate the efficacy and safety of bromfenac ophthalmic solution 0.09% (Xibrom™, ISTA Pharmaceuticals Inc., Irvine, CA, USA) for treating pain associated with corneal ulcers. ***Methods:*** Twenty-five eyes of 24 patients with corneal infiltrates (bacterial or fungal) were treated with appropriate anti-infective agents along with bromfenac twice daily for up to 102 days to treat the pain caused by the infection. Follow-up visits were frequent in the first 2 weeks upon initiation of treatment, then at least weekly until infections were resolved. The best corrected visual acuity, location, size, and density of corneal infiltrates, the size and presence of a corneal epithelial defect, subjective eye pain (scale of 0-4) and time to pain resolution, the ability to conduct daily activities, and adverse events were recorded at each follow-up visit. The results of these treated patients were compared with those of 10 control eyes with corneal infiltrates (bacterial or fungal) where appropriate anti-infectives were used without adjunct medications. ***Results:*** Fifty-two percent of bromfenac-treated patients reported no pain by day 3, compared with 0% of untreated controls (P=0.023). Most of the treated patients' epithelium healed by day 20 (68%) compared with only 10% of controls (P=0.040). Most bromfenac-treated patients (71%) returned to normal activities within 2 days of starting treatment with bromfenac, compared with 0% of controls (P=0.018). No adverse events were recorded. ***Conclusion:*** Bromfenac was effective in treating pain associated with infectious keratitis and did not delay corneal epithelialization nor cause any corneal adverse events in this group of 25 eyes.

Keywords: bromfenac; cornea; keratitis; ulcer; Xibrom

INTRODUCTION

Infectious keratitis is caused by bacterial, viral, or fungal penetration of the cornea's defense system. In ulcerative keratitis (corneal ulcer), the corneal epithelial layer is disrupted, exposing the stroma with nerve endings beneath, causing symptoms such as severe pain, red eye, tearing, purulent discharge, blurred vision, and/or eyelid

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swelling. Pain due to infectious keratitis may be quite debilitating, causing sleep disturbances and disruption in completing normal daily tasks. Topical corticosteroids are prescribed to treat a variety of ocular inflammations; however, their safety and efficacy in treating inflammation and pain is controversial,[1,2] and is still being evaluated. The extended use of steroids are associated with an increased incidence of adverse events, including the formation of cataract, elevated intraocular pressure, delayed wound healing of the corneal epithelia and stroma, and increased susceptibility to infections.[3,4]

Ophthalmic nonsteroidal anti-inflammatory drugs (NSAIDs) have been shown to provide effective pain relief for traumatic corneal abrasions, with minimal adverse events.[5-8] NSAIDs produce their anti-inflammatory and analgesic effects via inhibition of cyclooxygenase (COX) activity, which, in turn, halts prostaglandin synthesis. Prostaglandins are responsible for a variety of systemic and localized inflammation, including ocular tissue inflammation.[9] Currently, there are four topical ophthalmic NSAIDs approved by the United States Food and Drug Administration (FDA) for the treatment of postoperative inflammation after cataract surgery: diclofenac sodium,[10] ketorolac tromethamine,[11] nepafenac,[12] and bromfenac ophthalmic solution 0.09% (Xibrom™, ISTA Pharmaceuticals Inc., Irvine, CA, USA).[13] Bromfenac has also been approved by the FDA for the reduction or treatment of ocular pain after cataract surgery.[13]

A combined analysis of two phase 3 randomized, placebo-controlled clinical trials showed that bromfenac completely cleared ocular inflammation after cataract extraction in 64% of patients, while placebo cleared inflammation in 43% of patients at study day 15.[14] The mean time to ocular pain resolution was 2 days versus 5 days for bromfenac and placebo, respectively. Notably, the adverse effects were lower in the group receiving bromfenac than in the placebo group.[14]

The present study was specifically designed to clinically evaluate the efficacy and safety of bromfenac 0.09% for treating pain associated with corneal ulcers.

MATERIALS AND METHODS

The study protocol was approved by the central internal review board for the investigational site, and the study was conducted in accordance with the principles stated in the Declaration of Helsinki. Written informed consent was obtained from all patients before initiation of study-specific procedures.

Study Population

All patients agreed to keep all required follow-up appointments, and to avoid disallowed medications, such as systemic or topical NSAIDs (except for the study medication), steroids, anticoagulants, or other medications prohibited by the protocol. Patients were excluded if they had a history of known hypersensitivity to bromfenac and salicylates.

Study Design

The present study was a prospective and nonrandomized clinical trial. Twenty-four corneal ulcer patients with 25 infected eyes were sequentially enrolled and the next 10 sequential eyes were selected as untreated historical controls. At study entry, patients' baseline ophthalmic and medical histories were recorded, and their ocular infiltration was assessed to determine the Summed Ocular Inflammation Score. Patients were treated with appropriate anti-infective agents (after culture

and sensitivities were obtained) along with bromfenac, self-administered twice daily for up to 102 days as a single drop to the study eye. Follow-up visits were frequent in the first 2 weeks upon initiation of treatment, then at least weekly until infections resolved. The best corrected visual acuity, location, size, and density of corneal infiltrates, the size and presence of a corneal epithelial defect, subjective eye pain (scale of 0-4) and time to pain resolution, the ability to conduct daily activities, and adverse events were recorded at each follow-up visit.

Study Drug

Bromfenac ophthalmic solution was provided as a sterile aqueous solution. Each milliliter of bromfenac contained 1.035 mg bromfenac sodium equivalent to 0.9 mg bromfenac free acid. Concomitant medications were either Zymar® (gatifloxacin, Allergan Inc., Irvine, CA, USA), Vigamox® (moxifloxacin, Alcon Inc., Fort Worth, TX, USA), fortified gentamycin, fortified vancomycin, oral itriconazole, or natamycin.

Study Endpoints

The primary endpoint of the present study was the time to resolution of corneal infiltration. Additional endpoints were the time to corneal epithelium healing, time to pain resolution, and time to return to normal daily activities. The safety endpoint was the incidence of all adverse events throughout the treatment.

Statistical Analysis

Statistical analyses were performed using StatView statistical software (SAS Institute, Cary, NC, USA). The time-to-event analysis (survival analysis), such as the time to resolution of infectious keratitis and pain, and the time to return to normal daily activities were compared with nonparametric tests and Kaplan-Meier survival curves. Summary statistics for safety endpoints were calculated.

RESULTS

Patient Demographics and Disposition

Eligible patients were male or female, aged between 17 and 89 years, with ulcerative keratitis. Informed consent was obtained for the first patient on August 1, 2006, and the last patient completed the end-of-study assessments on March 22, 2007. All 24 patients received at least 2 weeks of bromfenac treatment in the infected eye twice daily. The mean (±SD) age of patients was 51.6±23.6 years, and 12 (50%) were female (Table 1).

Table 1. Baseline demographics.

	Bromfenac (0.09%)
Patients, *n*	24
Eyes, *n*	25
Female, *n* (%)	12 (50%)
Age, years	
Mean±SD	51.6±23.6
Range	17-89

Figure 1. Kaplan-Meier survival curve for time to healing.

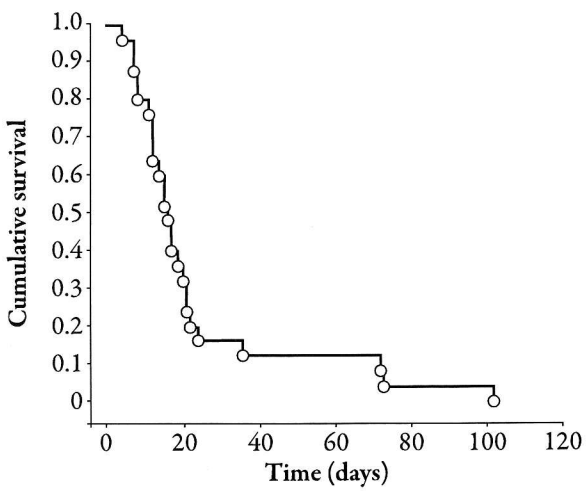
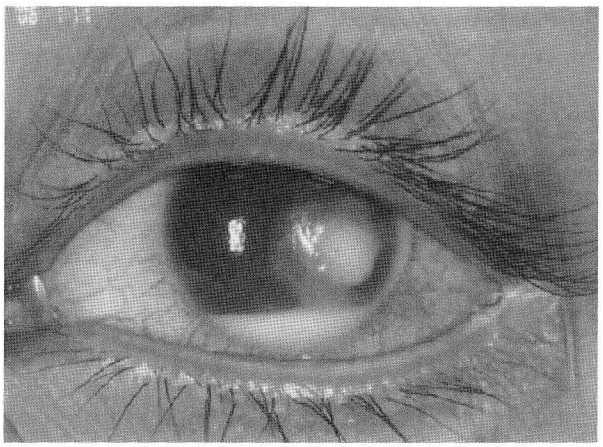


Figure 2. Images of eyes of a 17 year old patient with infiltration and healed eye: (**A**) with fungal corneal ulcer prior to treatment, and (**B**) posttreatment with topical anti-fungal drops plus bromfenac twice daily.

(A)



(B)

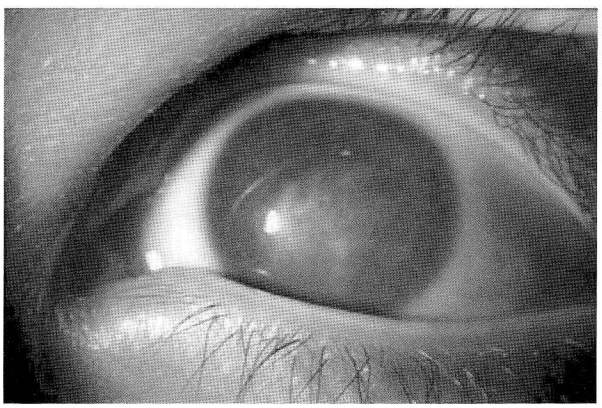
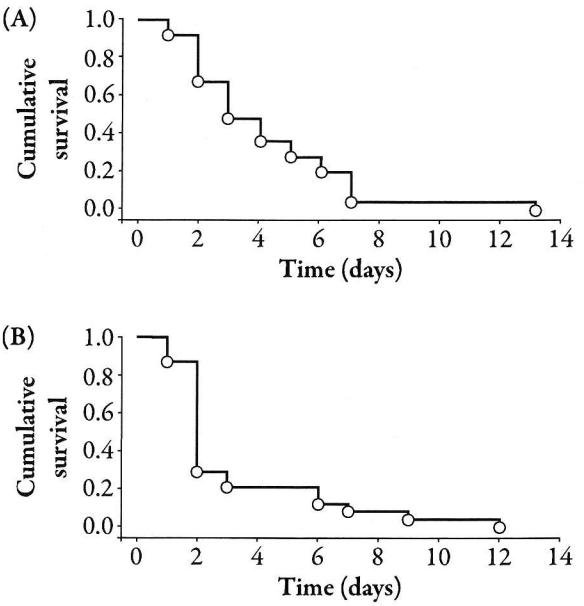


Figure 3. Kaplan-Meier survival curves for (**A**) time to pain resolution, and (**B**) time to return to normal daily activities.



Primary Endpoint (Time to Healing)

The primary endpoint was the mean (±SD) time to resolution of infection. Ocular infiltration resolved in 23.4±23.7 days, with a range of 4 to 102 days in treated patients, with median of 16 days (Figure 1). In the control group, mean time to resolution of infiltration was 32.5 days (P=0.054). Sixty-eight percent (17/25) of infected and treated eyes were resolved by day 20 (Figure 2), compared with 60% (6/10) of controls (P=0.120).

Additional Endpoints (Epithelial Healing, Pain Resolution, Return to Normal Daily Activities)

Analyses of additional endpoints were performed using the same statistical tools. In treated patients, mean (±SD) time to pain resolution was 4.16±2.69 days, with a range of 1 to 13 days, and the median was 3 days. In untreated patients, mean time to pain resolution was significantly greater, with a mean of 23.0 days (range: 15-38 days; P=0.004). In treated patients, 52% (13/25) of eyes had no pain by day 3, compared with 0% of untreated patients (P=0.023, Figure 3). Most of the treated patients' epithelium healed by day 20 (68%) compared with only 10% of controls (P=0.040).

Mean (±SD) time to return to regular daily activities (as reported by patients) was 3.2±2.8 days, with a range of 1 to 12 days,

and the median was 2 days in treated patients. Conversely, mean time to return to regular daily activities in controls was 25.8 days (range 5-135 days, $P<0.001$). Seventy-one percent (17/24) of patients returned to normal activities within 2 days of starting treatment with bromfenac, whereas no controls achieved this goal ($P=0.018$).

Safety

Bromfenac treatment in this group of 25 eyes did not cause any corneal adverse events.

DISCUSSION

Bromfenac ophthalmic solution 0.09% was effective in treating pain associated with corneal ulceration, and corneal epithelialization was within normal range in this group of 25 eyes. Furthermore, no corneal adverse events were observed.

In ulcerative keratitis, the denuded epithelium may also heal naturally. When epithelial cells divide, new cells cover the bare cornea until the ulcer is healed. In a normal cornea, an epithelial defect heals relatively quickly, typically within 2 weeks. Evidence has shown that without treatment the time to corneal epithelium healing in guinea pig is about 10 days.[15] Furthermore, after complete de-epithelization, approximately 80% of the corneal epithelial surface is healed.[4] While steroids aid in reducing ocular pain, they have been shown to retard epithelium healing.[4] In the present study, similar to other NSAIDs, bromfenac did not delay corneal wound healing. It is important to note, however, that the safety and efficacy of any NSAID for the treatment of corneal ulcers in patients with Sjogren's syndrome has not been established.

The anti-inflammatory and analgesic effects of NSAIDs are produced by COX inhibition. Various NSAIDs differ in their potency against COX-1 and COX-2. Among the current NSAIDs, bromfenac has been shown to be the most potent ophthalmic NSAID in inhibiting the COX-2 enzyme.[16] Furthermore, the dosing of bromfenac is more convenient compared to other NSAIDs. The FDA-approved dosing for bromfenac is twice daily, while other NSAIDs are often administered three or four times a day.

CONCLUSION

Bromfenac was effective in treating pain associated with infectious keratitis and did not delay corneal epithelialization nor cause any corneal adverse events in this group of 25 eyes.

ACKNOWLEDGMENTS

Previous Presentation

This work was previously presented in part at the American Society of Cataract and Refractive Surgery annual meeting in San Diego, CA, from April 27 to May 2, 2007.

Declaration of Interest

Dr. Barry A. Schechter and Dr. Trattler are consultants for Allergan, ISTA and on the speakers board for Inspire.

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