A Retrospective Surveillance Study of Besifloxacin Ophthalmic Suspension 0.6% in the Treatment of Bacterial Keratitis

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BACKGROUND

- Treatment of bacterial keratitis has traditionally consisted of fortified antibacterial agents or a combination of topical antibacterial agents to provide better antimicrobial activity against infectious agent(s).
- Fourth-generation fluoroquinolones are broad-spectrum antibiotics that are effective monotherapeutic alternatives to this paradigm.[1-4]
- A recent treatment update characterized fourth generation fluoroquinolones as the standard of care for management of small corneal defects (up to 2 mm in size).[5]

1. Wilhelmus KR, Hyndiuk RA, Caldwell DR, et al. 0.3% ciprofloxacin ophthalmic ointment in the treatment of bacterial keratitis. *Arch Ophthalmol.* 1993;111:1210-8. 2. O'Brien TP, Maguire MG, Fink NE, et al. Efficacy of ofloxacin vs cefazolin and tobramycin in the therapy for bacterial keratitis: report from the Bacterial Keratitis Study Research Group. *Arch Ophthalmol* .1995;113:1257-65. 3. Ofloxacin Study Group. Ofloxacin monotherapy for the primary treatment of microbial keratitis: a double-masked, randomized, controlled trial with conventional dual therapy. *Ophthalmology.* 1997;104:1902-9. 4. Constantinou M, Daniell M, Snibson GR, Vu HT, Taylor HR. Clinical efficacy of moxifloxacin in the treatment of bacterial keratitis. *Opthalmology.* 2007;114:1622-1629. 5. Miller D. Pharmacological treatment for infectious corneal ulcers. *Expert Opin Pharmacother.* 2013;14:543-60.

PURPOSE

- Besifloxacin ophthalmic suspension 0.6% (Besivance®) is indicated for the treatment of bacterial conjunctivitis.[1] In the clinical trials, high eradication rates were observed against infections attributed to those species that are common pathogens in bacterial keratitis, including *P. aeruginosa*.[2]
- Besifloxacin exhibits good ocular pharmacokinetics[3] and was effective in previous animal models of keratitis.[4-5]
- The objective of this study was to evaluate the safety of besifloxacin ophthalmic suspension 0.6% when used in the treatment of bacterial keratitis.

1. Besivance®(besifloxacin ophthalmic suspension) 0.6% prescribing information, 09/2012. 2. Silverstein BE, Morris TW, Gearinger LS, et al. Besifloxacin ophthalmic suspension 0.6% in the treatment of bacterial conjunctivitis patients with *Pseudomonas aeruginosa* infections *Clin Ophthalmol.* 2012;6:1987-96. 3. Proksch JW et al (2009) Ocular pharmacokinetics of besifloxacin following topical administration to rabbits, monkeys, and humans. *J Ocul Pharmacol Ther.* 25(4):335–44. 4. Sanders ME et al (2011) Comparison of besifloxacin, gatifloxacin, and moxifloxacin against strains of Pseudomonas aeruginosa with different quinolone susceptibility patterns in a rabbit model of keratitis. *Cornea.* 30(1):83–90. 5. Sanders ME et al (2009) Efficacy of besifloxacin in a rabbit model of methicillin-resistant Staphylococcus aureus keratitis. *Cornea*. 28(9):1055–60.

Methods

- Multicenter, retrospective, surveillance of bacterial keratitis cases where either topical besifloxacin ophthalmic suspension 0.6% or moxifloxacin ophthalmic solution 0.5% were prescribed.
- Investigators provided case information on outcomes and reported any adverse events (AEs) related to the antibacterial used using an Electronic Data Collection form.
- Treatment outcomes included evidence of corneal scarring, corneal neovascularization, investigator's assessment of bacterial eradication, visual acuity (VA) before and after treatment, and duration of pain.
- The primary endpoint was the incidence of adverse drug reactions.

RESULTS

- 227 consecutive case reports (227 eyes: 142 besifloxacin, 85 moxifloxacin) were obtained from 10 clinical sites in the U.S.
- Demographics were similar across treatment groups. Mean age was 39.5 (range, 11-96) years for the besifloxacin group and 41.0 (range, 16-91) years for the moxifloxacin group, and the majority were female.
- More than half of patients wore contact lenses, and most (>60%) had small corneal lesions (<10% of corneal surface).
- Median duration of antibiotic treatment was 15 days in both treatment groups; roughly a third of patients were treated with a maximum dose frequency of five or more times per day.

RESULTS CONT.

- There was only 1 drug-related ocular AE reported: a case of mild superficial punctuate keratitis in a patient treated with besifloxacin and another antibacterial for a large corneal ulcer. The case resolved without scarring or neovascularization.
- There were no differences between treatments in rates of bacterial eradication (>90% in both groups, P=0.208)
- There were no differences between treatments in rates of corneal scarring, corneal neovascularization, duration of pain ($P \geq 0.302$).
- Visual acuity findings before and after treatment demonstrated similar improvements in both groups with no difference in the distribution of final visual acuity (P=0.311).

DEMOGRAPHICS

	Besifloxacin (n=142)	Moxifloxacin (n=85)
Age at first day of treatment, y		
Mean (SD)	43.9 (21.2)	42.9 (20.5)
Median (range)	39.5 (11-96)	41.0 (16-91)
Gender, n (%)		
Male	53 (37.3)	37 (43.5)
Female	89 (62.7)	48 (56.5)
Contact lens wear, n (%) *		
None	61 (43.0)	35 (41.2)
Soft, Daily	47 (33.1)	32 (37.6)
Soft, Extended	26 (18.3)	8 (9.4)
Soft, Continuous	3 (2.1)	5 (5.9)
Rigid	0	2 (2.4)
Relevant etiologic factors, n (%)		
Trauma or prior corneal surgery**	9 (6.3)	17 (20.0)
Aqueous tear deficiency	8 (5.6)	5 (5.9)
Immunodeficiency	1 (0.7)	2 (2.4)
Recent corneal disease	8 (5.6)	4 (4.7)
Malposition of eyelids	3 (2.1)	1 (1.2)
Other	9 (6.3)	2 (2.4)
Unknown	43 (30.3)	32 (37.6)

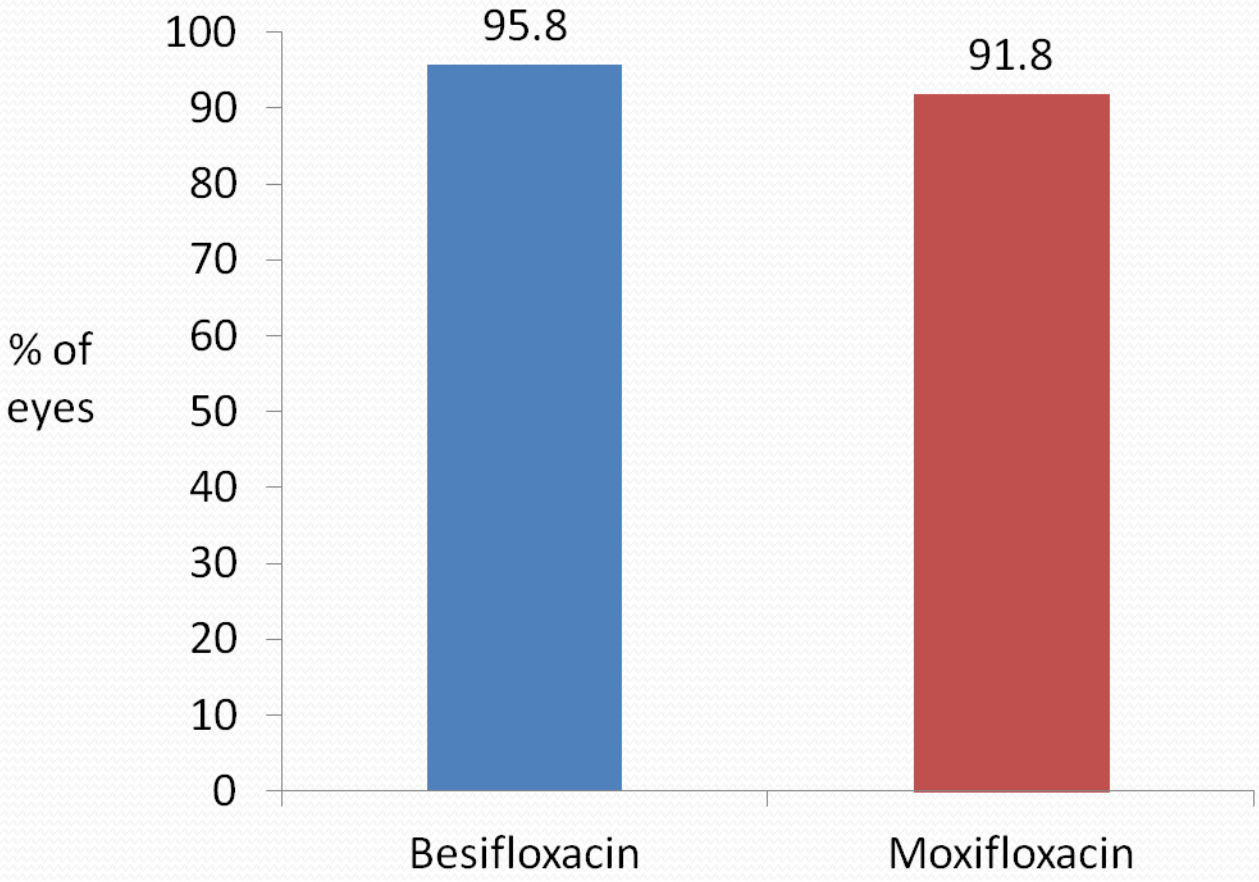
* Contact lens data not available for 5 subjects in each treatment group

** *P*=0.001 for the difference between treatments. There were no other differences between treatments in etiologic factors.

Dosing Frequency & Duration

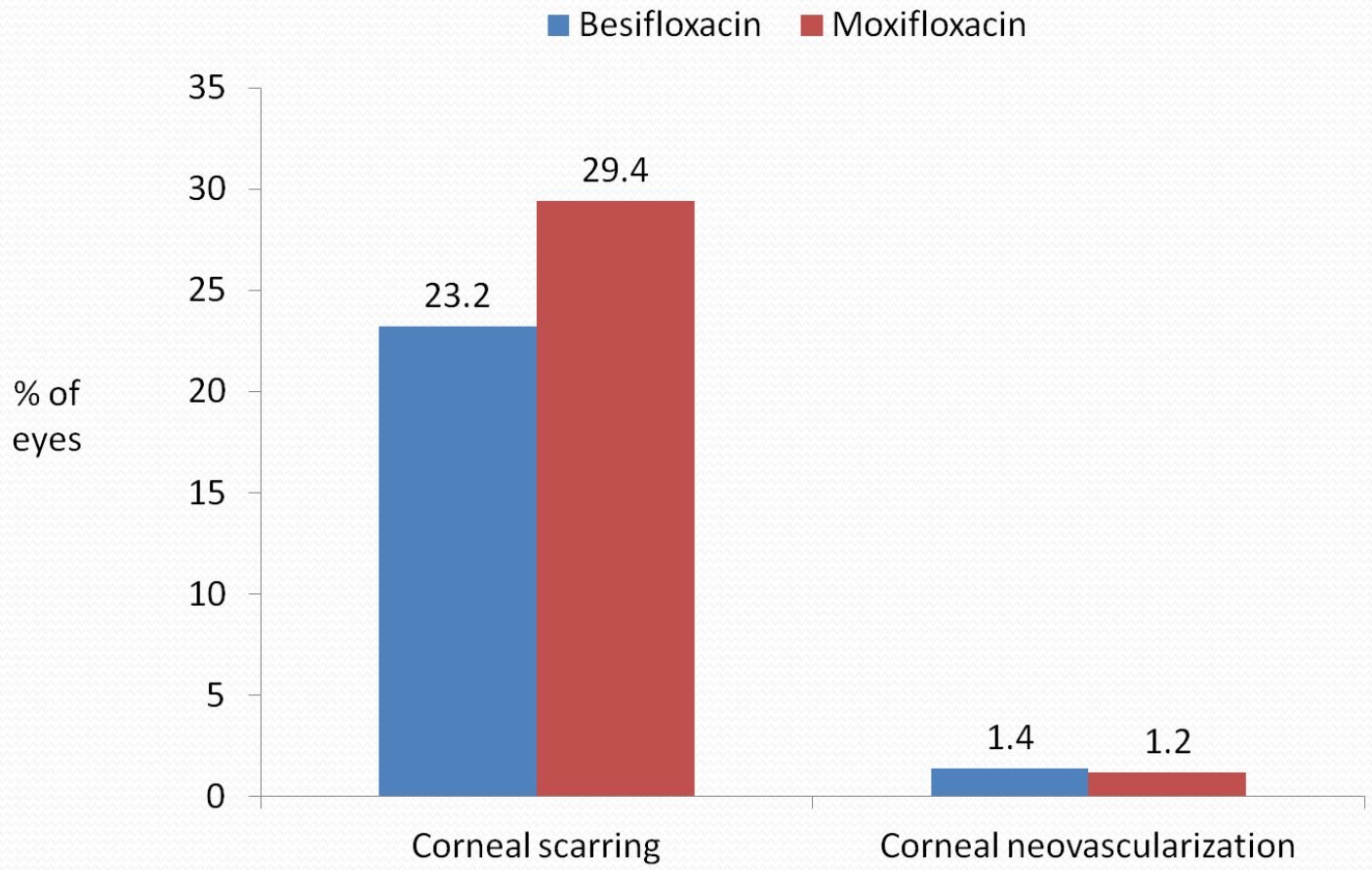
	Besifloxacin (n=142)	Moxifloxacin (n=85)
Maximum frequency of antibacterial use, n (%)		
1 time daily	1 (0.7)	1 (1.2)
2 times daily	5 (3.5)	5 (5.9)
3 times daily	9 (6.3)	8 (9.4)
4 times daily	60 (42.3)	24 (28.2)
5 to 8 time daily	21 (14.8)	15 (17.6)
>8 times daily	12 (8.5)	11 (12.9)
Data missing	34 (23.9)	21 (24.7)
Duration of antibacterial use, days		
Mean (SD)	23.6 (27.5)	28.2 (49.6)
Median (range)	15 (3-200)	15 (2-380)
Final frequency of antibacterial use, n (%)		
1 time daily	1 (0.7)	1 (1.2)
2 times daily	5 (3.5)	5 (5.9)
3 times daily	10 (7.0)	9 (10.6)
4 times daily	61 (43.0)	25 (29.4)
5 to 8 time daily	21 (14.8)	15 (17.6)
>8 times daily	10 (7.0)	9 (10.6)

% SUCCESSFUL BACTERIAL ERADICATION

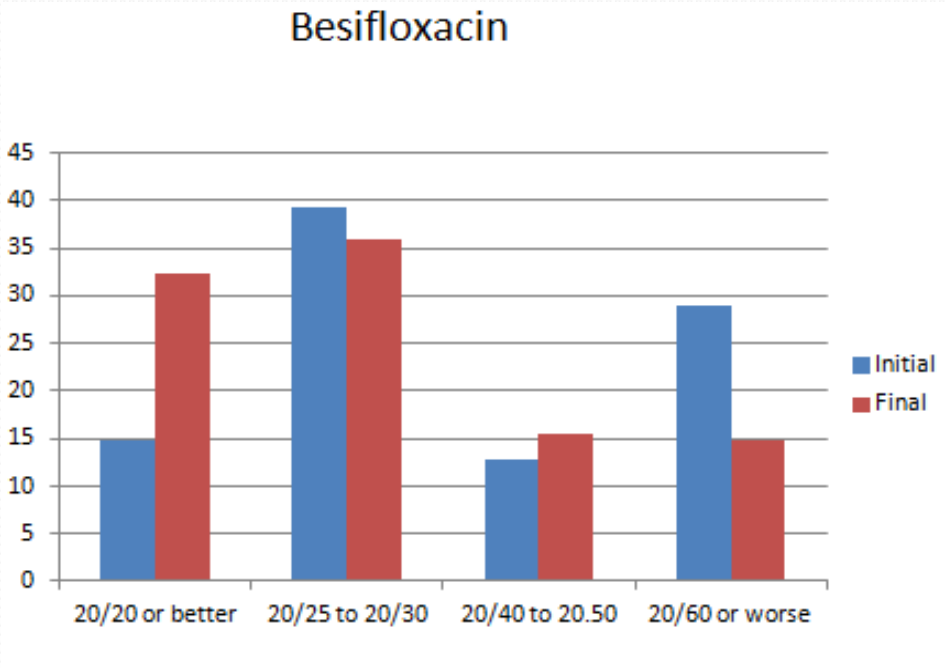


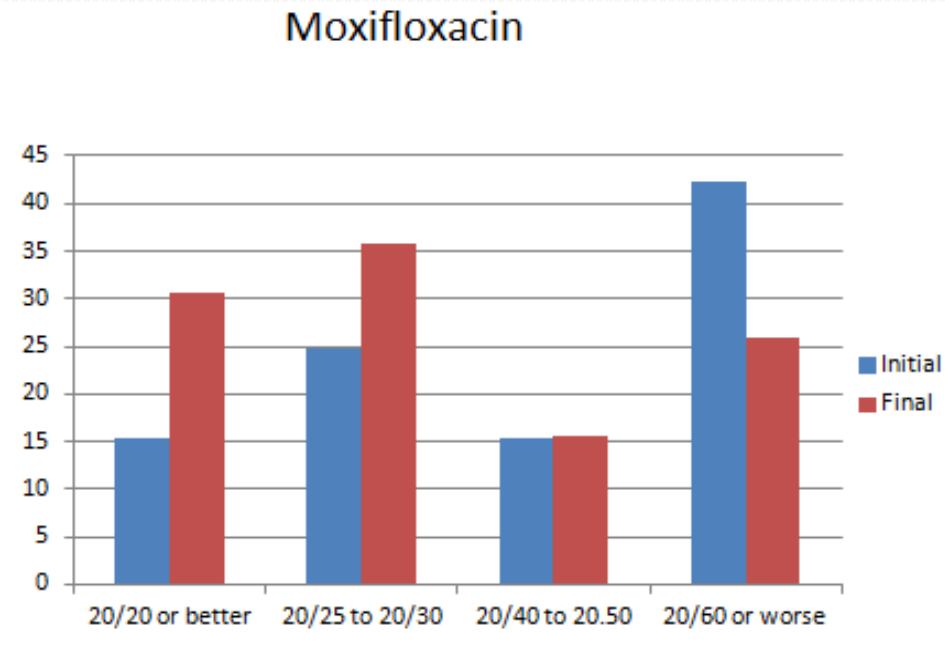
*Bacterial eradication was evaluated by the investigator

Rates of Corneal Scarring and Corneal Neovascularization



VISUAL ACUITY: BEFORE & AFTER





CONCLUSIONS

- This retrospective surveillance data suggest that besifloxacin ophthalmic suspension 0.6% was well tolerated for treatment of keratitis with no significant adverse drug reactions.
- Bacterial eradication, corneal scarring, corneal neovascularization, duration of pain, and final visual acuity were similar between besifloxacin and moxifloxacin treatment groups.
- These safety findings are consistent with those reported in larger prospective, controlled studies of besifloxacin when used to treat bacterial conjunctivitis.[1-4]

1. Karpecki P, DePaolis M, Hunter JA, et al. Besifloxacin ophthalmic suspension 0.6% in patients with bacterial conjunctivitis: a multicenter, prospective, randomized, double-masked, vehicle-controlled, 5-day efficacy and safety study. *Clin Ther*. 2009;31:514-26. 2. McDonald MB, Protzko EE, Brunner LS, et al. Efficacy and safety of besifloxacin ophthalmic suspension 0.6% compared with moxifloxacin ophthalmic solution 0.5% for treating bacterial conjunctivitis. *Ophthalmology*. 2009;116:1615-23. 3. Tepedino ME, Heller WH, Usner DW, et al. Phase III efficacy and safety study of besifloxacin ophthalmic suspension 0.6% in the treatment of bacterial conjunctivitis. *Curr Med Res Opin*. 2009;25:1159-69. 4. DeLeon J, Silverstein BE, Allarie C, et al. Besifloxacin ophthalmic suspension 0.6% administered twice daily for 3 days in the treatment of bacterial conjunctivitis in adults and children. *Clin Drug Investig.* 2012;32:303-17.