BESIVANCE® (besifloxacin ophthalmic suspension) 0.6%: A Potent Broad-spectrum Fluoroquinolone for the Treatment of Bacterial Conjunctivitis

Francis S. Mah, MD

ABSTRACT  As bacteria develop resistance to the drugs we use to treat infection, we need increasingly potent antibiotics to keep them in check. BESIVANCE® (besifloxacin ophthalmic suspension) 0.6% is a fluoroquinolone with a number of appealing features.


*Efficacy for this organism was studied in fewer than 10 infections.

Among the things that distinguish besifloxacin are its low minimum inhibitory concentrations (MICs) against many of the bacteria of concern to ophthalmologists, including methicillin-resistant staphylococci, and its ability to remain on the eye for a prolonged period of time. These combine to make BESIVANCE® an excellent agent for the treatment of bacterial conjunctivitis. Several factors account for the potency of besifloxacin: its balanced activity against DNA gyrase and topoisomerase IV and its dual halogenation. Because bacterial conjunctivitis is often treated empirically—without knowledge of the causative organism or its susceptibility—the chances of success can be maximized when a potent, broad-spectrum antibiotic is used. Balanced activity, low MICs against organisms of greater concern, and the ability to remain on the eye all argue strongly for the use of BESIVANCE® in the treatment of bacterial conjunctivitis. The clinical significance of in vitro data is not known.

Important Safety Information about BESIVANCE®

- BESIVANCE® is for topical ophthalmic use only, and should not be injected subconjunctivally, nor should it be introduced directly into the anterior chamber of the eye.

- As with other anti-infectives, prolonged use of BESIVANCE® may result in overgrowth of non-susceptible organisms, including fungi. If super-infection occurs, discontinue use and institute alternative therapy.

- Patients should not wear contact lenses if they have signs or symptoms of bacterial conjunctivitis or during the course of therapy with BESIVANCE®.

- The most common adverse event reported in 2% of patients treated with BESIVANCE® was conjunctival redness. Other adverse events reported in patients receiving BESIVANCE® occurring in approximately 1-2% of patients included: blurred vision, eye pain, eye irritation, eye pruritus and headache.

- BESIVANCE® is not intended to be administered systemically. Quinolones administered systemically have been associated with hypersensitivity reactions, even following a single dose. Patients should be advised to discontinue use immediately and contact their physician at the first sign of a rash or allergic reaction.

- Safety and effectiveness in infants below one year of age have not been established.
The Importance of In Vitro Potency

Antibiotic potency is an important key to dealing with both actual and potential resistance. The commonly accepted measure of in vitro potency is a drug's minimum inhibitory concentration (MIC), the concentration at which that drug can inhibit the in vitro growth of a specific isolate. The classic metrics of potency are the MIC50 and MIC90, which represent the lowest concentration at which a drug inhibits 50% and 90%, respectively, of tested isolates of a given species.

All other things being equal, the lower a drug's MIC, the more bacteria that can be eliminated with exposure to the drug. The greater the number of bacteria killed or inhibited, the fewer the number of survivors with a chance to mutate and become resistant. So in vitro potency—as demonstrated by low MICs—is important in an antibiotic. That said, the true clinical significance of in vitro data is not known, and in vitro studies have demonstrated cross-resistance between BESIVANCE® and other fluoroquinolones.

In Vitro Potency of Besifloxacin

Taking a close look at besifloxacin, it demonstrates very low MICs against relevant ocular pathogens (Table 1).1,6

The MIC values shown in Table 1 are important because most cases of bacterial conjunctivitis are treated empirically—we initiate treatment without knowing the causative organism or its susceptibility. The drug with the greatest ability to eradicate organisms of interest is found by looking at MIC50 values. As can be seen from the low MIC50 values in Table 1, besifloxacin has in vitro potency against these resistant staphylococci—important gram-positive pathogens in ophthalmology. The clinical significance of in vitro data has not been established.

In addition, BESIVANCE® is indicated for the treatment of bacterial conjunctivitis caused by P. aeruginosa. While all members of the quinolone family have been successfully used to treat gram-negative infections, the FDA label recognizes the ability of BESIVANCE® to address this important pathogen capable of causing serious damage to the eye.7 A specific indication from the FDA may be important for the many physicians outside ophthalmology who treat bacterial conjunctivitis but may be less familiar with ophthalmic pharmaceuticals.

Sources of In Vitro Potency: Balanced Action

Fluoroquinolones work by inhibiting two enzymes that are critical for bacterial replication: DNA gyrase and topoisomerase IV.1 The original quinolones bound DNA gyrase, with relatively little effect on topoisomerase IV.5 Since DNA gyrase inhibition has a disproportionately greater effect on gram-negative bacteria, the early quinolone antibiotics had relatively less efficacy against gram-positive organisms.8

Succeeding generations of quinolones have had greater affinity for topoisomerase IV; indeed, besifloxacin has well balanced activity against both DNA gyrase and topoisomerase IV.1 The strong affinity of besifloxacin for topoisomerase IV has been demonstrated to result in low MIC50 values against resistant gram-positive S. aureus and S. pneumoniae (Table 1).1 A balanced targeting of both enzymes may also slow the emergence of resistance to besifloxacin, since this would require two separate bacterial mutations.10

In vitro resistance to BESIVANCE® occurs at a general frequency of < 3.3 × 10^{-10} for S. aureus and < 7 × 10^{-10} for S. pneumoniae.10

Sources of In Vitro Potency: Dual Halogenation

In addition to the fluorine atom common to all fluoroquinolones, besifloxacin has a second halogen substitution, a chlorine, on its molecule. Halogenation has long been used to modulate the activity of drugs, and in the case of besifloxacin that halogenation appears to contribute to its increased affinity for topoisomerase IV, increasing its potency.9 Additionally, the drug’s 7-azepinyl ring distinguishes it from other fluoroquinolones. This functional group also contributes to its potency.11

Before the development of besifloxacin, other chlorofluoroquinolones had been formulated, some of which were extremely potent, but most of which were deemed too toxic for systemic medical application.7 A topical ophthalmic agent, BESIVANCE® emerged as a broad-spectrum bactericidal antibiotic that has high potency and an established safety profile in topical ophthalmic application.

On-eye Staying Power

BESIVANCE® (besifloxacin ophthalmic suspension) 0.6% is formulated to eradicate organisms on the surface of the eye. BESIVANCE® is prepared with a mucoadhesive polymer vehicle designed to prolong the drug’s residence time on the ocular surface; besifloxacin remains on the eye for close to 24 hours.12 At 12 hours, the concentration is above the MIC50 of several significant ocular pathogens (Figure 1).2,6,12 Recommended dosing for BESIVANCE® is TID, with 4 to 12 hours between each dose.10

Reasons to Treat Bacterial Conjunctivitis

Although it does not often cause severe morbidity, there are good reasons to treat bacterial conjunctivitis. A 2005 study estimated that 4 million cases of bacterial conjunctivitis occur per year.

Table 1 Minimum inhibitory concentrations of besifloxacin against ciprofloxacin-resistant S. aureus and S. epidermidis. (Source: Adapted from Reference 6.) Clinical significance of in vitro data has not been established.

<table>
<thead>
<tr>
<th>Organism</th>
<th>MIC (µg/mL)</th>
<th>MIC50</th>
<th>MIC90</th>
</tr>
</thead>
<tbody>
<tr>
<td>MSSA–CR (n = 14)</td>
<td>0.5–2</td>
<td>0.5</td>
<td>1</td>
</tr>
<tr>
<td>MRSA–CR (n = 15)</td>
<td>0.5–16</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>MSSE–CR (n = 9)</td>
<td>0.5</td>
<td>0.5</td>
<td></td>
</tr>
<tr>
<td>MRSE–CR (n = 13)</td>
<td>0.5–8</td>
<td>0.5</td>
<td>4</td>
</tr>
</tbody>
</table>

* Due to the limited isolates, only the MIC50 value is given.

Abbreviations:
year in the US, with the total cost to households of lost wages, and to society of lost work reaching over 500 million dollars.\textsuperscript{13}

It is also important to treat bacterial conjunctivitis because some conjunctivitis is caused by bacteria that are capable of producing significant damage to the eye. Since conjunctivitis is rarely cultured, we typically do not know which bacterial species we are dealing with. An infection caused by \textit{P. aeruginosa}, for example, can be limited to the conjunctiva upon initial presentation, but can progress to far more serious disease.

\section*{Why In Vitro Potency Matters}

What do we need in a medication to treat bacterial conjunctivitis? First, to cover a range of possible pathogens, it must have broad-spectrum activity. The fluoroquinolones—including besifloxacin with its activity against indicated gram-negative and gram-positive organisms—meet this criterion. Again, because it is not routine to culture in cases of conjunctivitis, any given case may be caused by a highly susceptible, highly resistant, or intermittently susceptible organism—we simply don’t know. But a potent, broad-spectrum antibiotic like besifloxacin can be effective in many of these scenarios.

\section*{Conclusion}

It is important to treat bacterial conjunctivitis with a potent and broad-spectrum antibiotic. BESIVANCE\textsuperscript{®}, an ophthalmic chlorofluoroquinolone, is potent and has balanced activity against bacterial DNA gyrase and topoisomerase IV. It has been shown to have in vitro potency against resistant bacteria, including MRSA and MRSE. Formulated in a vehicle for prolonged residence time on the eye, BESIVANCE\textsuperscript{®} is a potent agent for the treatment of bacterial conjunctivitis.

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\section*{References}

Besivance®
besifloxacin ophthalmic suspension, 0.6%

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use Besivance safely and effectively. See full prescribing information for Besivance.
Besivance® (besifloxacin ophthalmic suspension) 0.6%, is a quinolone antiinfective indicated for the treatment of bacterial conjunctivitis caused by susceptible isolates of the following bacteria:
*Efficacy for this organism was studied in fewer than 10 clinical trials.

4 CONTRAINdications
Avoidance of Contact Lenses
Prolonged Use

5 WARNINGS AND PRECAUTIONS

5.3 Avoidance of Contact Lenses
Patients should not wear contact lenses if they have symptoms of bacterial conjunctivitis or staining.

1 INDICATIONS AND USAGE
FULL PRESCRIBING INFORMATION

1.1 INDICATIONS
The mean besifloxacin Cmax was 0.37 ng/mL on day 1 and 0.43 ng/mL on day 6. The average elimination half-life of besifloxacin in plasma following multiple dosing was estimated to be 7 hours.

12.4 Microbiology
Besifloxacin is an 8-fluoroquinoline with a fluoro-N1-phenyl ring. The compound has activity against Gram-positive and Gram-negative bacteria due to the inhibition of both bacterial DNA gyrase and topoisomerase IV. DNA gyrase is an essential enzyme required for replication, transcription and repair of bacterial DNA. Topoisomerase IV is an essential enzyme required for partitioning of the chromosomal DNA during bacterial cell division. Besifloxacin is bactericidal with minimum bacterial concentrations (MBCs) generally within one dilution of the minimum inhibitory concentrations (MICs). The mechanism of action of fluoroquinolones, including besifloxacin, is different from that of aminoglycosides, macrolides, and l-flactam antibiotics. Therefore, besifloxacin may be active against pathogens that are resistant to these antibacterials and these antibacterials may be active against pathogens that are resistant to fluoroquinolones. In vitro studies demonstrated cross-resistance between besifloxacin and other fluoroquinolones.

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14 CLINICAL STUDIES
In a randomized, double-masked, vehicle controlled, multicenter clinical trial, in patients 1-9 years of age who had 1 or 2 eyes affected, Besivance was superior to vehicle in patients with bacterial conjunctivitis. Clinical resolution was achieved in 45% (90/198) for the Besivance treated group versus 33% (63/191) for the vehicle treated group (difference 12%, 95% CI 0.0% - 22%). Microbiological outcomes demonstrated a statistically significant eradication rate for causative pathogens of 41% (78/191) for the Besivance treated group versus 67% (128/191) for the vehicle treated group (difference 26%, 95% CI 23% - 40%). Microbiologic eradication does not always correlate with clinical cure.

16 HOW SUPPLIED/STORAGE AND HANDLING

16 Storage:

17 PATIENT COUNSELING INFORMATION
Patients should be advised to avoid contaminating the applicator tip with material from the eye, fingers or other surfaces.

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