Topical ophthalmic fourth-generation fluoroquinolones: Appropriate use and cost considerations

Richard G. Fiscella, Charles C. Lewis, and Michael K. Jensen

Many hospital formularies have restrictions on the use of systemic antibiotics. Clinicians are allowed to prescribe certain antiinfectives only when culture and sensitivity data have demonstrated resistance to formulary antibiotics or when appropriate empirical antibiotic coverage is indicated. Such restrictions help ensure that the use of more potent and expensive antibiotics is appropriate, while reducing concerns for increased resistance from overuse.

Considerations for the appropriate use of topical ophthalmic antibiotics are different. Prophylaxis and treatment may initially require the most broad-spectrum coverage available to prevent or treat potentially vision-threatening infections. The topical ophthalmic fourth-generation fluoroquinolones have wide antibacterial coverage, demonstrate excellent pharmacokinetics and pharmacodynamics, are efficacious, and are safe and well tolerated. They exhibit broad-spectrum activity against key ocular pathogens, including *Staphylococcus epidermidis* and *Staphylococcus aureus*, *Streptococcus* species, the anaerobe *Propionibacterium acnes*, and many gram-negative organisms. They also provide some activity against other significant emerging pathogens (e.g., atypical mycobacteria). The fourth-generation topical ophthalmic fluoroquinolones are one of a few classes of antimicrobials that penetrate both the aqueous

**Purpose.** The utilization and refill rates of topical ophthalmic fourth-generation fluoroquinolones among physicians, as well as the associated costs, were studied.

**Methods.** A large data set of retrospective pharmacy prescription claims was obtained from multiple plans, including commercial managed care organizations, Medicaid, and Medicare. The data included the number and cost of all new and refill prescriptions for six months for gatifloxacin 0.3% and moxifloxacin 0.5% by physician specialty. New prescription and refill data were also analyzed from a state Medicaid plan to determine if similar trends existed.

**Results.** Primary care physicians wrote approximately 7,000 (7.7%) gatifloxacin and 84,000 (92.3%) moxifloxacin prescriptions, with pediatricians accounting for 4,000 (5.1%) gatifloxacin and 75,000 (94.9%) moxifloxacin prescriptions. Eye care physicians accounted for a similar amount of prescriptions for each antibiotic during the same period. The total cost of prescriptions for all primary care practitioners was approximately $170,000 for gatifloxacin and $2.5 million for moxifloxacin; prescriptions written by pediatricians accounted for $110,000 for gatifloxacin and $2.2 million for moxifloxacin.

**Conclusion.** Prescription drug claims from payers using pharmacy benefit management companies during a six-month period indicated that the numbers of prescriptions written for gatifloxacin and moxifloxacin were similar among eye care physicians, but primary care physicians wrote a greater number of prescriptions for moxifloxacin. Analysis of claims to a Medicaid database revealed an increase in the prescriptions written by primary care physicians for moxifloxacin after its addition to the drug formulary.

**Index terms:** Costs; Drug use; Gatifloxacin; Moxifloxacin; Ophthalmic preparations; Prescribing; Quinolones; Rational therapy

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and vitreous fluids after systemic administration. Fourth-generation fluoroquinolones exhibit less resistance to certain pathogens (e.g., coagulase-negative staphylococci, S. aureus) than do third-generation fluoroquinolones.\(^1\)

The use of fourth-generation topical ophthalmic fluoroquinolones should be reserved for the prophylaxis and treatment of vision-threatening infections, such as bacterial keratitis. Reports of inappropriate use of these agents for non-vision-threatening infections are a concern, specifically overuse by pediatricians and some family practitioners when treating presumed bacterial conjunctivitis.\(^2\)

The numbers of plans, the geographic capability, given that most states have differences in acquisition cost based on contract prices.

**Results**

Data for 4,019,626 prescription claims obtained from September 2005 through February 2006 were analyzed. A total of 154 provider specialties were identified in the data set. The mean ± S.D. number of patients receiving all topical ophthalmic prescriptions each month was 682,000 ± 27,000.

**Primary care physicians** (i.e., family practitioners, general practice, internists, pediatricians, obstetrician-gynecologists) wrote 7,021 gatifloxacin and 84,169 moxifloxacin prescriptions over the six-month period (Table 1). Of the primary care physicians, pediatricians accounted for 4,465 gatifloxacin and 75,023 moxifloxacin prescriptions. Eye care physicians (ophthalmologists and optometrists) wrote a similar amount of gatifloxacin (152,145) and moxifloxacin (138,070) prescriptions (Table 1).

The mean ± S.D. actual amount paid by the insurer per prescription was $21.15 ± $1.30 for gatifloxacin 0.3% solution (Zymar, Allergan) and moxifloxacin 0.5% solution (Vigamox, Alcon Laboratories) were reviewed. Because of the number of prescription plans included in the data set, the formulary status for the two drugs was not available. The data requested included the prescribing physician’s specialty and whether the prescription was a new or refill prescription. The actual paid claim cost per specialist and cost for refills were also obtained. Cost data were based on the actual amount paid by the insurer. The ingredient cost and dispensing fees were compared for the two drugs to eliminate any aberrant benefit designs that might skew use or reimbursement amounts. The mean amount paid per prescription represented the mean acquisition cost across the various types of plans from which the data were obtained (e.g., commercial, Medicaid, Medicare). Two-tailed Student’s \(t\) test for paired data was used to analyze ingredient costs, dispensing fees, and copayments for each drug. A comparison of costs based on the wholesale acquisition cost (WAC) was also computed.

New prescription and refill data were also analyzed from a state Medicaid plan (IMS Exponent Plantrak, Plymouth Meeting, PA) to determine if the results and trends from the commercial managed care organization were similar. Results from the Illinois Department of Public Aid are reported before and after formulary inclusion of both drugs. Prescribing data for all physician types were obtained for three months before formulary inclusion (October through December 2005) and for five months after formulary inclusion (January through May 2006). The WAC was used for comparison because it would have more widespread applicability, given that most states have differences in acquisition cost based on contract prices.

**Methods**

The prescription claims data set was solicited from the Pharma Solutions Business Unit of Wolters Kluwer Health in Phoenix, Arizona. No constraints were placed on the sources of the prescription claims information; however, the claims data were to include information for ophthalmic preparations only. The data set included 4,019,626 prescriptions for ophthalmic medications prescribed over a six-month period. Wolters Kluwer Health obtained the claims data from commercial managed care organizations, managed Medicaid programs, managed Medicare programs, self-funded employer groups, and any other payers that used pharmacy benefit management companies (PBMs) to adjudicate pharmacy claims. The data were blinded as to the source of claims, so the numbers of plans, the geographic locations, and the number of covered lives are unknown. Because the prescription claims data contained no patient identifiers, institutional review board approval was not required for the study.

The prescription data for gatifloxacin 0.3% solution (Zymar, Allergan) and moxifloxacin 0.5% solution (Vigamox, Alcon Laboratories) were reviewed. Because of the number of prescription plans included in the data set, the formulary status for the two drugs was not available. The data requested included the prescribing physician’s specialty and whether the prescription was a new or refill prescription. The actual paid claim cost per specialist and cost for refills were also obtained. Cost data were based on the actual amount paid by the insurer. The ingredient cost and dispensing fees were compared for the two drugs to eliminate any aberrant benefit designs that might skew use or reimbursement amounts. The mean amount paid per prescription represented the mean acquisition cost across the various types of plans from which the data were obtained (e.g., commercial, Medicaid, Medicare). Two-tailed Student’s \(t\) test for paired data was used to analyze ingredient costs, dispensing fees, and copayments for each drug. A comparison of costs based on the wholesale acquisition cost (WAC) was also computed.

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for primary care physicians and $193,200.00 for pediatrians. The total cost of moxifloxacin (based on a WAC of $48.30 as of July 2006) would be $4,057,200.00 for primary care physicians and $3,622,500.00 for pediatrians.

The total cost of prescriptions written by eye care physicians was $3,217,489.92 and $3,305,725.74 for gatifloxacin and moxifloxacin, respectively.

The number of refills dispensed was 14,377 for gatifloxacin and 19,913 for moxifloxacin among all prescribers ($<0.001). This reflected a 28% higher refill rate for moxifloxacin than for gatifloxacin. The number of refills for prescriptions written by eye care physicians was 12,932 for gatifloxacin and 14,484 for moxifloxacin ($=0.003). The number of refills for prescriptions written by primary care physicians was 1,445 for gatifloxacin and 5,429 for moxifloxacin ($<0.001).

The total amount paid for moxifloxacin refills over the six-month period was 41% greater ($518,335.39) than for gatifloxacin ($304,073.55) based on the average actual amount paid by the insurer per prescription. The total cost of refills for all prescribers using the WAC would be $694,409.10 for gatifloxacin and $961,797.90 for moxifloxacin. The total cost for refills prescribed by eye care physicians using the WAC would be $69,793.50 for gatifloxacin and $262,220.70 for moxifloxacin.

Before either medication was on the formulary of the Illinois Department of Public Aid, pediatrians prescribed two bottles of gatifloxacin and seven bottles of moxifloxacin from October through December 2005. As of January 2006, when both drugs were available on the formulary, prescribing by all physician types from January through May 2006 was 6,464 bottles of moxifloxacin and 992 bottles of gatifloxacin, of which eye care physicians accounted for 662 and 672 bottles prescribed, respectively (IMS Exponent Plantrak). During that same five-month period, pediatrians prescribed 3,715 bottles of moxifloxacin and 143 bottles of gatifloxacin. Costs for drugs prescribed by pediatrians using WAC pricing would be $179,434.50 for moxifloxacin and $6,906.90 for gatifloxacin.

Eight months after moxifloxacin’s removal from preferred drug list of the formulary, prescriptions written by primary care physicians for moxifloxacin decreased from a mean of 1293 per month to just 41 per month. During that same period, prescriptions written by primary care physicians for gatifloxacin increased from a mean of 198 per month to 261 per month.

Discussion
Waiting for culture and sensitivity tests to confirm a diagnosis of bacterial keratitis or endophthalmitis before prescribing broad-spectrum topical ophthalmic antibiotics may result in increased ocular morbidity and possible blindness. Bacterial keratitis and endophthalmitis are considered vision-threatening diseases that can cause severe ocular tissue damage within hours. In the treatment of bacterial keratitis, the American Academy of Ophthalmology’s (AAO’s) preferred practice pattern suggests initial treatment with fluoroquinolones or cefazolin and fortified aminoglycosides administered every half hour or every hour. In fact, if gram-positive organisms are found using Gram’s stain, treatment with fourth-generation fluoroquinolones, vancomycin, or cefazolin ophthalmic drops is recommended. Results of one recent study demonstrated that gatifloxacin was the preferred alternative to ciprofloxacin as first-line monotherapy for the treatment of keratitis. A significantly higher percentage of bacterial ulcers in the gatifloxacin-treated group exhibited complete healing than in the ciprofloxacin-treated group (95.1% versus 80.9%, respectively) ($=0.042). Gatifloxacin was also more effective against gram-positive cocci than was ciprofloxacin. Since fluoroquinolones are commercially available as ophthalmic preparations and do not need to be extemporaneously compounded, as do cefazolin, fortified aminoglycosides, and vancomycin, they have become the preferred treatment for bacterial keratitis.

Prophylaxis during ophthalmic surgeries also requires the use of

<table>
<thead>
<tr>
<th>Table 1. Comparison of Prescription Volumes and Costs for Gatifloxacin and Moxifloxacin Ophthalmic Solutions Based on Prescriptions Written by Primary Care Physicians and Eye Care Physicians</th>
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</thead>
<tbody>
<tr>
<td><strong>Drug and Physician Specialty</strong></td>
</tr>
<tr>
<td><strong>Gatifloxacin</strong></td>
</tr>
<tr>
<td>All prescribers</td>
</tr>
<tr>
<td>Ophthalmologists and optometrists</td>
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<tr>
<td>Primary care physicians</td>
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<td>All pediatrians</td>
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Notes: Topical ophthalmic fluoroquinolones
broad-spectrum antibiotics with minimal resistance. Ocular pathogens, particularly gram-positive cocci and coagulase-negative staphylococci, cause up to 94% of postoperative cases of endophthalmitis. Endophthalmitis, although rare, frequently results in poor vision. Recently, increased resistance of coagulase-negative staphylococci endophthalmitis isolates to fourth-generation fluoroquinolones was reported, raising concerns about whether these agents provide adequate coverage against postoperative pathogens. Postoperative prophylaxis with certain fluoroquinolones may reduce the risk of endophthalmitis. The efficacy and safety of the postoperative use of topical ophthalmic antibiotics should be considered important elements in the prophylaxis of surgical infections.

A possible contributor to this reported increase in resistance is the inappropriate use of fourth-generation fluoroquinolones for what are often considered non-vision-threatening infections. Infectious conjunctivitis may have various etiologies including viral and bacterial organisms. Bacterial conjunctivitis is often caused by Streptococcus pneumoniae, Haemophilus influenzae, and S. aureus. Systemic treatment may be required for more severe forms, especially neonatal conjunctivitis (e.g., gonococcal, H. influenzae, diphtheritic). AAO has concluded that most bacterial conjunctivitis is mild and will resolve spontaneously without specific treatment in immunocompetent adults. AAO has indicated that the duration, recurrence, and morbidity associated with bacterial conjunctivitis may be decreased if treated for five to seven days with the least expensive broad-spectrum antibiotic indicated. Bacterial conjunctivitis should be treated with a cost-effective, well-tolerated, broad-spectrum topical ophthalmic antibiotic, such as polymyxin–trimethoprim or polymyxin–bacitracin ointment.

The average wholesale prices for gatifloxacin, moxifloxacin, and commonly used generically available topical ophthalmic antibiotics are provided in Table 2.

One systematic review and meta-analysis of topical ophthalmic antibiotics versus placebo for acute bacterial conjunctivitis found that topical ophthalmic antibiotics are associated with improved rates of early clinical remission (days 2–5); the benefit is marginal for later remission (days 6–10). A large, multicenter, randomized, controlled study conducted over four years assessed three different strategies for managing acute infective conjunctivitis, including immediate antibiotic (chloramphenicol) use, no antibiotic use, and delayed (3 days) antibiotic use, in 307 patients. Prescribing strategies did not affect the symptom severity, but the duration of moderate symptoms was shorter with antibiotic treatment (4.8 days for no antibiotic, 3.3 days for immediate antibiotic use, and 3.9 days for delayed antibiotic use).

Data obtained from a prescription database (Verispan 2006) demonstrated that family practitioners and pediatrics treated conditions such as conjunctivitis and blepharitis with topical antibiotics 86% of the time. Although gatifloxacin and moxifloxacin are indicated for the treatment of bacterial conjunctivitis, eye care physicians were more likely to use these antiinfectives for vision-threatening infections. Up to 51% of topical antiinfectives prescribed by eye care physicians were for the prevention of serious eye infections in ocular surgery (e.g., cataract surgery); 15% of antiinfectives were prescribed for the treatment of corneal ulcers and eye injury.

The results of the current study indicate general practitioners (pediatricians and family practitioners) prescribe moxifloxacin more often than do eye care physicians, who tend to have higher prescribing rates for gatifloxacin. We believe that detailing practices by the various manufacturers may contribute to the higher prescribing rates of moxifloxacin by general practitioners. Alcon has 240 representatives to promote its products, including moxifloxacin 0.5% solution, to primary care physicians; Allergan, the manufacturer of gatifloxacin 0.3% solution, has no representatives promoting its products to primary care practitioners (Verispan’s Sales Force Structure and Strategies Sales Force Sizes, first quarter of 2006).

The costs to health plans and Medicaid observed in this study were much higher with moxifloxacin. In our analysis, the total cost of prescriptions for all primary care practitioners was $170,000 for gatifloxacin and $2.5 million for moxifloxacin and for pediatrics was $110,000.

### Table 2. Cost Comparison of Ophthalmic Antimicrobial Products Based on Average Wholesale Price (AWP)*

<table>
<thead>
<tr>
<th>Ophthalmic Product</th>
<th>Container Size</th>
<th>AWP ($)</th>
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<tbody>
<tr>
<td>Moxifloxacin</td>
<td>3-mL bottle, 78 drops/bottle</td>
<td>60.38</td>
</tr>
<tr>
<td>Gatifloxacin</td>
<td>5-mL bottle, 137 drops/bottle</td>
<td>60.38</td>
</tr>
<tr>
<td>Trimethoprim–polymyxin</td>
<td>10-mL bottle, 244 drops/bottle</td>
<td>17.42</td>
</tr>
<tr>
<td>Bacitracin</td>
<td>3.5-g ointment</td>
<td>4.75</td>
</tr>
<tr>
<td>Polymyxin–bacitracin</td>
<td>3.5-g ointment</td>
<td>25.77</td>
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*Wholesale acquisition cost = $48.30.
for gatifloxacin and $2.2 million for moxifloxacin. These costs were obtained from the actual costs paid by the health plan.

To determine whether these findings were consistent in other settings, relevant data from the Illinois Department of Public Aid were retrieved. Review of these data revealed that when neither medication was on the formulary, pediatricians prescribed only a few bottles of either drug. When both drugs were added to the formulary in January 2006, prescribing rates for all physicians types increased for the next five months, to over 6000 bottles of moxifloxacin and less than 1000 for gatifloxacin. Eye care physicians prescribed slightly more than 650 of each drug. Pediatricians prescribed over 3700 bottles of moxifloxacin and less than 150 bottles of gatifloxacin. Based on the increased prescribing of these agents after addition to the drug formulary, inappropriate use is an important concern, as is the cost of newer agents, which is dramatically higher than previously used generic topical ophthalmic antibiotic formulations.

**Conclusion**

Prescription drug claims from payers using PBMs during a six-month period indicated that the numbers of prescriptions written for gatifloxacin and moxifloxacin were similar among eye care physicians, but primary care physicians wrote a greater number of prescriptions for moxifloxacin. Analysis of claims to a Medicaid database revealed an increase in prescriptions written by primary care physicians for moxifloxacin after its addition to the drug formulary.

**References**