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Gatifloxacin Ophthalmic Solution for Treatment of Bacterial Conjunctivitis: Safety, Efficacy and Patient Perspective

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Abstract: Gatifloxacin is a fourth generation fluoroquinolone antibiotic that has been prescribed for systemic use. However, the drug which was developed by Kyorin (Japan) was linked to toxic reactions and death and was banned in the United States and Canada for use as an oral dosage form. It continues to be used as a topical application for ophthalmic conditions as the systemic toxicity seen when taking the drug orally has not been observed with ophthalmic use. The available data indicate that ocular use of gatifloxacin is safe, and effective against a broad spectrum of bacteria, including intracellular bacteria and anaerobes.

Keywords: Antibiotic, ophthalmic, drug, anti-bacterial, topical

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Introduction

Gatifloxacin is a member of the fluoroquinolone antibiotic family.¹ It is approved for treatment of bacterial conjunctivitis caused by a broad range of microorganisms.^{2,3} As with other members of this group it functions by inhibiting the bacterial enzymes DNA gyrase and topoisomerase IV. This design for fourth generation fluoroquinolones theoretically enables them to reduce the opportunity for microbial resistance to the antibiotic.² The former designation for this molecule was AM-1155.² It was developed by Kyorin Pharmaceutical Co., Ltd., Tokyo, Japan. It is marketed as Zymar in the United States (Allergan, Irvine, CA) and as Gatiflo in Japan (Senju, Osaka). Zymar was introduced in 2003 for the treatment of bacterial conjunctivitis. Bacterial conjunctivitis may be characterized as an inflammation of the conjunctiva. It is due to pyogenic bacteria and is accompanied by symptoms such as irritation of the conjunctiva which may be generally noticed on other parts of the eye, impaired vision, pain which may be extreme and a mucopurulent exudate. In untreated cases the infection may lead to loss of the eye. Treatment of this condition is by aggressive topical antibiotic therapy and sometimes steroids.

Anti-microbial Spectrum/Efficacy

Gatifloxacin and other fluoroquinolones are effective against a broad spectrum of bacteria that may cause ocular infections in humans including endophthalmitis and conjunctivitis.⁴ Melo et al found that gatifloxacin was effective against a range of both Gram positive and Gram negative microorganisms including anaerobes when tested in vitro.⁴ It is designed as a once daily dosing therapy for bacterial exacerbation of acute inflammatory disease. Unfortunately it is also been associated with systemic toxicity in humans.⁵⁻⁷ These data may be confirmed by a more recent Indian study in 756 patients where gatifloxacin showed a broad range of activity against both Gram negative and Gram positive bacteria.⁸ Moriyama and Hfling-Lima demonstrated upon retrospective analysis of 239 patients with contact lens induced keratitis that gatifloxacin was effective at controlling *Pseudomonas* isolates indicating use against a common water borne microbial hazard to contact lens wearers.⁹ A study done by Durairaj et al found that when gatifloxacin was delivered to the surface of the eye by a

dendrimeric polyguanidylated translocation system there was enhanced solubility of the antibiotic and rapid entry into the corneal epithelial spaces. Thus, it is possible to deliver the drug topically by more than one mechanism.¹⁰ Gatifloxacin has also been formulated with a combination of sodium alginate and sodium carboxymethyl cellulose as an alternative to eye drops. It was found that a sustained release was achieved over a 12 hour period with the antibiotic remaining active against both *S. aureus* and *E. coli*.¹¹

Chemistry

The chemical formula for gatifloxacin is $C_{19}H_{22}FN_3O_4$. The antibiotic has a protein binding efficiency of 20% and a half-life of (maximum) 14 hours. It is a 6-fluoro-8-methoxy quinolone. The molecular mass of the antibiotic is 375.394 g/mol. The molecule has a 3-methylpiperazine at the position 7 of the quinolone ring and a methoxy group at position 8. The mechanism of killing action is not dependant on bacterial life cycle.¹² These data show that gatifloxacin will kill both stationary and active growth phase *E. coli* and staphylococci.

Toxicology and Safety

One of the early papers on AM-1155 (gatifloxacin) concerning the effect of the drug on intracellular bacteria such as *Mycobacterium tuberculosis* was published in 1993.¹ Tomioka et al showed that AM-1155 (1 μ g/mL) completely inhibited intracellular growth of this bacteria. It was found to be superior to ofloxacin in this respect.¹ There have been several other studies which have discussed the anti-microbial and toxicological patterns and issues with gatifloxacin. Gatifloxacin was evaluated in the presence and absence of benzalkonium chloride (BAK, 50 mg/mL).¹³ The data show that gatifloxacin required at least 120 minutes in the absence of BAK to be effective at reducing a broad spectrum of microbial activity. These experiments included *S. pneumoniae*. With BAK present that anti-microbial activity time was reduced to 5 minutes or less. This suggests that BAK may be the major factor in reduced microbial counts. In contrast, McCracken showed that gatifloxacin was effective at reducing *S. pneumoniae* concentrations in a rabbit model.¹⁴ In this case BAK was not present. Dawis and colleagues showed that gatifloxacin was an effective synergistic agent



with piperacillin, cefepime and meropenem against selected agents with at a 50% reduction in bacterial counts as compared to control values.¹⁵ Hosaka used gatifloxacin (called AM-1155 in this paper) as an antimicrobial agent against a broad spectrum of microbes including *Staphylococcus aureus*, *P. aeruginosa* and *N. gonorrhoeae*.² Kato used AM-1155 against a broad range of anaerobic organisms including Clostridium species.¹⁶ These organisms were clinical isolates, the exception being the *Bacteroides fragillis* group. Hoshi et al found that gatifloxacin was superior to levofloxacin against methicillin-resistant *S. aureus* strains (in vitro) at concentrations of 2,048 µg/mL.¹⁷

Yamamoto and co-workers have shown that AM-1155 was passively transferred into murine macrophages and human polymorphonuclear (PMN) leukocytes in a biologically active form.¹⁸ AM-1155 (gatifloxacin) was able to reduce the levels of *S. aureus* by 95% when measured intracellularly. The authors speculated that this may be due to high intracellular concentrations. The available evidence suggests that AM-1155 was not bound upon transfer.

Pre-clinical

Ishiwata and co-workers showed in male Wistar rats (diabetic) that systemic administration of gatifloxacin (50 or 100 mg I.V.) lead to increased secretion of epinephrine. This in turn lead to an increase in serum glucose levels relatively rapidly.¹⁹ The serum epinephrine concentration reached a peak at 0.25 hours following administration of gatifloxacin.

Gatifloxacin was found to be superior to ceftriaxone and vancomycin in treating a strain of *Streptococcus pneumoniae* in a rabbit model.²⁰ Perrig et al introduced the penicillin-resistant strain of *S. pneumoniae* into the cisterna magna of New Zealand White rabbits.²⁰ The authors also found that when cefepime was added to gatifloxacin and given as a cocktail that killing rates improved slightly. These data are consistent with in vitro experiments performed by these authors and by Dawis.¹⁵

Gatifloxacin has also been used in pre-clinical studies with CD-1 mice in the treatment of *Mycobacterium tuberculosis* infections.²¹ Gatifloxacin and moxifloxacin were evaluated in vitro and were found to have similar activities against *M. tuberculosis*. Neither drug was as effective as isoniazid (INH) in either in vitro or in vivo (mice) experiments. It should be noted that no

ocular toxic reactions were reported by any of these authors. Further, toxic reactions were not reported by Sugioka et al when studying penetration of gatifloxacin, levofloxacin and moxifloxacin into the ocular tissues of New Zealand White rabbits.²² This group was looking at the relative penetration rates of these three antibiotics when given as eye drops. They found that there were statistically significant differences comparing moxifloxacin with the other two drugs in terms of ability to penetrate to the cornea, aqueous humor and conjunctiva. These authors note that moxifloxacin is more highly hydrosoluble than either gatifloxacin or levofloxacin.

There have also been pre-clinical studies done in rabbits which were injected with gatifloxacin, gentamicin, and moxifloxacin.²³ Following intracameral injection (3 days) the eyes were harvested and compared to controls with central corneal thickness as the measurement. The data show a significant difference between the gentamicin treated eyes and the controls. No significant difference was noted between gentamicin, and gatifloxacin or moxifloxacin and controls, indicating that in this model with central corneal thickness as the marker, gatifloxacin use did not lead to toxicity. These authors also pointed out that for both central corneal thickness and comparison of scanning electron microscopy that gentamicin did cause significant toxic effects ($P < 0.05$) as compared to controls. Neither gatifloxacin nor moxifloxacin demonstrated statistical toxicity as compared to controls in this study. Sharma studied the topical application of gatifloxacin along with other fluoroquinolones such as norfloxacin, ciprofloxacin, lomefloxacin, sparfloxacin and moxifloxacin in a rat corneal burn model to determine the effects on matrix metalloproteinases (MMP) 2 and 9.²⁴ These MMPs have been implicated healing of corneal injury. The data show that gatifloxacin was not significantly different than other fluoroquinolones in delaying corneal regeneration.²⁴

Human Systemic Administration

The initial clinical reports of AM-1155 (gatifloxacin) were positive with no indications of extreme side effects.²⁵ Oral single and multiple dosing of the drug was reported to be well tolerated and found in detectable concentrations in saliva, serum and urine. Of the 30 volunteers who received the drug, no toxic or other adverse reactions were reported. However, case



reports began to surface concerning the safety and tolerability of the drug when given by a systemic route. A case report published in 2008 identified a link between gatifloxacin and rhabdomyolysis.²⁶ A 50 year old male patient was placed on gatifloxacin (I.V. 200 mg once daily) following hospital admission with intermittent fever and lower urinary tract symptoms. Renal complications ensued with the patient experiencing muscle pain and weakness. The patient was taken off gatifloxacin and placed on cefoperazone (1 g twice daily). After 24 hours the patient's condition had improved. Other observed adverse effects associated with gatifloxacin were nausea, headache, dyspepsia, loose stools, drowsiness, fever and rash when taken with other drugs such as rifampicin, isoniazid and pyrazinamide. Gatifloxacin absorption was decreased in the presence of these drugs.²⁷ However, gatifloxacin has been used successfully in children for the treatment of otitis media.²⁸ In this study by Pichichero et al, an analysis of 867 children (in four clinical trials) had a better than 90% treatment success rate, with the major reported side effect of vomiting.

Gatifloxacin has also been linked to heart attack in at risk patients.²⁹⁻³¹ Oral administration to patients with a known history of heart disease was reported to lead to torsades de pointes or ventricular fibrillation. In some of these reported cases death was the result.

Gatifloxacin has been linked to increased risk of both hypoglycemia and hyperglycemia.³²⁻³⁵ The mechanism of action appears to be due to vacuolation of pancreatic beta cells. This leads to reduced insulin levels and thus hyperglycemia. As a result gatifloxacin has been withdrawn from the North American sales markets, although it still can be sold for systemic use in the Far East. While other related antibiotics such as ciprofloxacin and moxifloxacin are used successfully in patients who have glucose homeostasis abnormalities, gatifloxacin is not recommended.³⁶

Ophthalmic Uses of Gatifloxacin

Gatifloxacin formulated either as Zymar or Gatiflo, was found to be effective at preventing bacterial infections. Liu et al used both gatifloxacin ophthalmic gel and ophthalmic solution in the treatment of cataract patients.³⁷ These investigators found that the maximum concentration of gatifloxacin for both treatment groups was observed at 60 minutes, but the active

concentration was found to be 4.3 times higher for the ophthalmic gel formulation as compared to the ophthalmic solution formulation. However, Gungor et al found that moxifloxacin penetrated to the aqueous humor better than gatifloxacin during cataract surgery.³⁸ For both antibiotics increased concentrations were dose dependent, meaning that the more of either antibiotic was added the more penetrated to the aqueous humor.

Arantes and co-workers found that gatifloxacin applied one hour before cataract surgery and for fourteen days after surgery was superior to ciprofloxacin relative to reducing the number of positive post-operative conjunctival cultures, thus reducing the possibility of post-operative infections.³⁹ Kim and Toma found that repeated use of antibiotics following intraocular injection will select for resistant strains of ocular flora.⁴⁰ These authors compared conjunctival cultures from antibiotic treated and untreated eyes. The antibiotics were azithromycin, gatifloxacin, ofloxacin, and moxifloxacin hydrochloride.

A study was conducted in Korea comparing Gatiflo and Vigamox (0.5% moxifloxacin) bilaterally in photorefractive keratectomy patients (PRK).⁴¹ These antibiotics were given post-operatively with epithelial healing rate, pain or visual acuity being markers in the study. The authors found no statistically significant differences in the treatment groups for any parameter measured. This is perhaps not surprising since these two drugs are anti-bacterial agents and not wound healing agents. What may be more significant in this study was that there were no reported differences in the ocular toxicity patterns reported for the two drugs. These data are in concert with other groups who have observed the two antibiotics relative to toxicity patterns. There were 44 patients involved in this study.

Gatifloxacin has been studied as a combination product with various other drugs. Blair et al performed a study in 30 corneal ulcer patients where half the study group was treated with Zymar or a masked placebo.⁴² The other half was treated with gatifloxacin plus 0.1% dexamethasone. The primary outcome of the study was reduction of ulcer size at 10 weeks based on digital photographs. There was no statistically significant difference between the two groups for this outcome. Secondary outcome was residual ulcer area by clinician estimate. This marker demonstrated a statistically significant difference when ulcer area was



compared between the two treatment groups with the steroid treated area being about half the size of the antibiotic only area. Campos et al used a fixed topical dose combination of gatifloxacin (0.3%) and prednisolone (1%) to treat LASIK patients post-operatively. This formulation was compared to dosing with the same concentrations separately, that is as two separate treatments from two bottles of product.⁴³ These authors found no difference in effectiveness or tolerability of the combination product as compared to the traditional therapy in the 97 patients that were studied. There was no statistically significant sign or inflammation and no difference in visual acuity between the two groups. Patients that have taken gatifloxacin ophthalmic solution have reported side effects as noted above. The major complaint though seems to be cost of the product.

Gong et al compared the efficacy of gatifloxacin to levofloxacin in 235 patients (235 eyes) in a double blind study I China.⁴⁴ These patients had been diagnosed with bacterial conjunctivitis. There was no statistical difference between the two antibiotic treatments, with the efficacy and bacterial clearance for both being around 93%. There was no statistical difference between the two groups for visual acuity or drug tolerance.

Side effects of topical ophthalmic gatifloxacin treatment include eye pain, blurred vision, conjunctival symptoms, swollen eyes or broken blood vessels in the eye, headache, altered or unpleasant taste, throat swelling and difficulty breathing. Not all patients have these symptoms but they have been noted. Many of these symptoms and sign are not unlike the bacterial conjunctivitis condition the drug was designed to treat.

Conclusion

While gatifloxacin has been withdrawn for systemic use in humans it is emerging as an important therapy for ocular use against a wide range of bacterial induced ocular adverse events.⁴⁵ The available information indicates that there is no ocular toxicity when the drug is given topically and in prescribed concentrations.

Data are somewhat mixed in terms of the gatifloxacin effectiveness spectrum as compared to other diseases but what does not seem to be in question is its effectiveness in controlling ocular bacterial disease. Continued monitoring of patients being treated with

gatifloxacin will provide evidence of any potential and here-to-for unseen adverse events syndrome associated with the use of the drug.

Author Contributions

Conceived and designed the experiments: Referenced Authors. Analysed the data: CLS. Wrote the first draft of the manuscript: CLS. Contributed to the writing of the manuscript: CLS. Agree with manuscript results and conclusions: CLS. Jointly developed the structure and arguments for the paper: CLS. Made critical revisions and approved final version: CLS. The author reviewed and approved of the final manuscript.

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