MODERN TREATMENT FOR BACTERIAL KERATITIS

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Annotation: Infectious keratitis is a potentially blinding ocular condition of cornea which can cause severe visual loss if not treated at early stage. If the appropriate antimicrobial treatment is delayed, only 50% of the eyes gain good visual recovery. It can be caused by bacteria, virus, fungus, protozoa, and parasites. The common risk factors for infectious keratitis include ocular trauma, contact lens wear, recent ocular surgery, preexisting ocular surface disease, dry eyes, lid deformity, corneal sensational impairment, chronic use of topical steroids, and systemic immunosuppression.

***Key words**: keratitis, antimicrobial treatment, bacteria, Staphylococcus aureus*

Relevance. The common pathogens include Staphylococcus aureus, coagulase-negative Staphylococcus, Pseudomonas aeruginosa, Streptococcus pneumonia and Serratia species. The majority of community acquired cases of bacterial keratitis resolve with empiric treatment and do not require culture [1-3]. Corneal scraping for culture and sensitivity is indicated for corneal ulcers that are large in size, central in location, extend from middle to deep stroma, associated with pain, simultaneous presence of anterior chamber reaction or hypopyon, poor vision, and presence of corneal abscess or unresponsive to broad spectrum antibiotic therapy [4-6]. Recent studies have shown increasing evidence of resistance of microbes to antimicrobial agents [7–9]. Microorganisms develop resistance due to chromosomal mutation, expression of latent chromosomal genes by induction or exchange of genetic material via transformation [9, 10]. This can cause continued progression of the disease process despite the use of broad

spectrum antibiotics. The purpose of this study was to review the newer treatments available for treating the infectious keratitis including those which are resistant to the antimicrobial therapy.

Materials and methods

Articles reporting the efficacies of using fourth-generation fluoroquinolones or photodynamic therapy in the treatment of infectious keratitis were selected and analyzed. During selection of the articles, prospective studies had a higher ranking than the retrospective studies, and clinical/in vivo studies had higher ranking than in vitro studies.

Infectious Keratitis

Corneal ulcer or infectious keratitis is a serious condition of cornea that requires prompt management. When a patient presents with the features of infectious keratitis, clinical history and detailed clinical examination guide to the category of high risk or low risk characteristics [3]. Presence of history of ocular trauma, contact lens use, preexisting ocular surface disease, history of long term or injudicious use of topical steroids, large size of ulcer, and central location of ulcer are considered to be high risk characteristics. According to the American Academy of Ophthalmology guidelines for bacterial keratitis, most of the cases of community acquired infectious keratitis respond to the empirical treatment with antibiotics. Corneal scraping is indicated for corneal ulcers that are large in size, central in location, extend from middle to deep stroma, associated with pain, simultaneous presence of anterior chamber reaction or hypopyon, poor vision, and presence of corneal abscess or unresponsive to broad spectrum antibiotic therapy [6]. The culture-guided approach consists of taking a sample of corneal tissue by corneal scraping or biopsy and performing microbiological tests to determine the type of bacterial organisms and their sensitivity to the particular group of antibiotics. However, empirical antibiotics will usually be started after microbiological specimens have been collected if there is clinical suspicion of infection.

Treatment

Fluoroquinolones are synthetic broad spectrum antibiotics. They inhibit DNA gyrase (topoisomerase II) and topoisomerase IV enzyme, which are key enzymes involved in DNA replication and transcription [11]. Inhibition of these enzymes will lead to bacterial cell death [12]. Topoisomerase IV is the main target for most Gram-positive bacteria. DNA gyrase on the other hand is the main target for Gram-negative bacteria [12]. Nalidixic acid, the first generation fluoroquinolone, was used to treat urinary tract infection. The increasing incidence of resistance to earlier generation fluoroquinolones pointed to the need of newer generation antibiotics [13, 14]. The second-generation fluoroquinolones include ciprofloxacin and ofloxacin; third-generation fluoroquinolones include levofloxacin, fourth-generation fluoroquinolones include moxifloxacin and gatifloxacin. The advances in molecular structures of fourth-generation fluoroquinolones, that is, moxifloxacin and gatifloxacin, resulted in inhibition of both DNA gyrase and topoisomerase IV in Gram-positive bacteria [15]. These changes increase the antibiotic potency against Gram-positive organisms while maintaining their broad spectrum activities against Gram-negative bacteria [12]. These structural modifications also reduce the risk of development of resistant organisms since two concomitant mutations are necessary for the development of resistance [16–18]. Furthermore, the structure of moxifloxacin is resistant to bacterial cells' efflux mechanism, thus enhancing its potency to kill bacteria [11]. Ophthalmic application of fluoroquinolones began in the 1990s when the second generation fluoroquinolones like ciprofloxacin and ofloxacin were available in topical form. They were used for the treatment of infectious keratitis and conjunctivitis [19, 20]. In this paper, we reviewed the literature and looked into the clinical use of fourth-generation fluoroquinolones in the treatment of infectious keratitis.

In Vitro Potency of Fluoroquinolones

The potency of antibiotics against bacteria is reflected by the minimum inhibitory concentration (MIC) obtained for different organisms during microbiological analysis. A drug with a low MIC for a particular organism means that it has a potent antibiotic effect on this particular organism. Kowalski et al.

determined the MIC90s of 177 bacterial keratitis isolates to ciprofloxacin, ofloxacin, levofloxacin, gatifloxacin, and moxifloxacin [21]. They found that the MIC90s for Gram-positive bacteria were significantly lower for fourth-generation fluoroquinolones than second- or third-generations, especially for fluoroquinolone-resistant Staphylococcus aureus (3.0 ug/mL in moxifloxacin and gatifloxacin versus 64.0 ug/mL in levofloxacin, ciprofloxacin, and ofloxacin). However, ciprofloxacin (2nd generation) is still better than the third-and fourth-generation fluoroquinolones against Gram-negative organisms including Pseudomonas aeruginosa (ciprofloxacin 0.125 ug/mL, ofloxacin 1.5 ug/mL, levofloxacin 0.5 ug/mL, moxifloxacin 0.75 ug/mL, gatifloxacin 0.38 ug/mL). Among the two fourth-generation fluoroquinolones, moxifloxacin demonstrated statistically lower MIC90s for most Gram-positive bacteria; gatifloxacin on the other hand was noted to have lower MIC90s for most Gram-negative bacteria [21]. Sueke et al. collected 772 bacterial isolates from cases of bacterial keratitis in multiple centers in the United Kingdom and tested against standard and new antibiotics [22]. Among the fluoroquinolones (ciprofloxacin, ofloxacin, levofloxacin, and moxifloxacin), moxifloxacin demonstrated the lowest MICs for both Gram-positive and Gram-negative bacteria [22]. Chawla et al. identified 292 bacterial isolates from consecutive cases of suspected bacterial keratitis and reviewed their microbiological response to cefazolin, tobramycin, gatifloxacin, and moxifloxacin [23]. Susceptibilities to moxifloxacin and gatifloxacin were similar: 92.8% and 95.5% of all the bacterial isolates were susceptible to moxifloxacin and gatifloxacin, respectively. Only 83.6% and 90.1% of the isolates were susceptible to cefazolin and tobramycin, respectively [23]. A few other studies have tried to look into the in vitro susceptibilities of bacterial isolates obtained from ocular infections such as blepharitis, conjunctivitis, keratitis, and endophthalmitis to the commonly prescribed antibiotics. Similar results regarding fluoroquinolones were obtained in these studies in which the fourth-generation fluoroquinolones were generally superior to other generations of fluoroquinolones in their actions on Gram-positive bacteria [24–27]. Though consistent results were obtained for

Gram-positive organisms among these studies, in the study by Oliveira et al., ciprofloxacin had lower MICs than the two fourth-generation fluoroquinolones for Gram-negative bacteria, especially for Pseudomonas species [27]. The results of in vitro studies may not be directly translated to clinical effectiveness because there are no susceptibility breakpoints for topically applied antibiotics to the eye.

Clinical Trials on Fluoroquinolones

Three clinical trials were found in the literature investigating on the clinical efficacy of the fourth-generation fluoroquinolones in treating infectious keratitis. The largest study was conducted by Constantinou et al. [28]. They recruited 229 patients with bacterial keratitis and randomized to three treatment groups, the moxifloxacin (1.0%) group, the ofloxacin (0.3%) group, and the combined fortified tobramycin (1.33%)/cefazolin (5.0%) group. All the patients were given hourly instillation of the topical antibiotics in the first 48 hours then tapered off according to the protocol until after the 7th day when frequency of instillation will be adjusted according to clinical response. Of the bacterial isolates obtained, none of them were resistant to moxifloxacin, 2.5% were resistant to ofloxacin, 2.8% to ciprofloxacin, 14.8% to cefazolin, 1.6% to tobramycin, and 17.5% to chloramphenicol. The cure rate, the mean time to cure, the clinical sign score, and the rate of serious complications were not significantly different among the three groups. Two patients reported stinging and one developed ulceration of the inferior bulbar conjunctiva after applying antibiotics eyedrops, all of them were from the fortified treatment group. None of these minor complications were noted in the fluoroquinolones monotherapy groups. Another study conducted by Parmar et al. compared the effect of topical gatifloxacin 0.3%, a fourth-generation fluoroquinolone, with ciprofloxacin 0.3%, a second-generation fluoroquinolone, for the treatment of patient with bacterial keratitis and ulcer size of at least 2 mm [29]. This study recruited a total of 104 patients randomized to the two treatment group, with in-patient hourly instillation of topical antibiotics until the ulcer began to heal with dosing frequencies adjusted accordingly. Culture results revealed that significantly larger proportion of both Gram-positive and Gram-negative bacteria

were susceptible to gatifloxacin than ciprofloxacin. 96.2% of Gram-positive cocci were susceptible to gatifloxacin versus 60.4% to ciprofloxacin; all Gram-positive bacilli were susceptible to gatifloxacin but only 75% were susceptible to ciprofloxacin; 92.9% of Gram-negative bacilli were susceptible to gatifloxacin compared to 85.7% to ciprofloxacin. Even for Pseudomonas aeruginosa, 87.5% were susceptible to gatifloxacin while only 75% were susceptible to ciprofloxacin. Clinically, 95.1% of patients in gatifloxacin group enjoyed good response and complete healing of ulcer, which was significantly higher than the ciprofloxacin group in which only 80.9% of patients had complete healing. The mean time taken for the ulcer to heal was similar in the two groups. The latest clinical study of these kinds was conducted by Shah et al. in 2010 [30]. A total of 61 patients were randomized to three groups comparing the clinical effects of moxifloxacin 0.5%, gatifloxacin 0.5%, and combined fortified tobramycin 1.3%/cefazolin 5% on bacterial keratitis. All the patients suffered clinically from bacterial keratitis with ulcer size between 2 mm and 8 mm. In this study, 46% of the subjects had eye injury before the episode. Topical antibiotics were instilled hourly for the first 48–72 hours and then tapered off according to the study protocol. Of the bacterial isolates tested, 5.2% were resistant to tobramycin and 10.4% were resistant to cefazolin. All isolates were susceptible to the two 4th generation fluoroquinolones under study. The cure rates of the fortified antibiotics group was 90% and of the gatifloxacin and moxifloxacin group 95%. However, the difference was not statistically significant. The mean duration to heal, the final visual acuity, and the size of the corneal opacities at the end of the study were also found to be statistically insignificant. Two patients complained of mild ocular discomfort after applying gatifloxacin. No other adverse effect was reported.

Conclusion

Topical fourth-generation fluoroquinolones, namely, moxifloxacin and gatifloxacin, are good alternatives to combination of fortified antibiotics in the management of infectious keratitis. They may be used as empirical therapies after corneal scraping has been performed. Low antibiotics resistances to these two

fluoroquinolones are expected in view of their structural modifications and dual inhibition mechanisms. However, since moxifloxacin and gatifloxacin may not be as potent as ciprofloxacin or tobramycin against Gram-negative organisms such as Pseudomonas aeruginosa, further studies are warranted to compare the response of Pseudomonas infections to these antibiotics before we can conclude that the new fluoroquinolones are as potent as the standard combination of fortified antibiotics in the management of infectious keratitis. To date, only a few papers in the literature have reported the effect of photodynamic therapy (collagen CXL) in the management of infectious keratitis. The results of these trials are promising and imply that this new treatment modality may be useful in the treatment of resistant infectious corneal ulcer or as an adjunct for standard antibiotic treatment. However, since all of the published studies regarding CXL as the treatment of infectious keratitis were either based on animals or small numbers of patients, larger scale randomized, controlled trials should be conducted to evaluate the additional beneficial effects of CXL in infectious keratitis on top of conventional topical antibiotics. Furthermore, more evidence is required before it will be advisable to use CXL as the first line treatment for infectious corneal ulcers.

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