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Fungal Keratitis Responsive to Moxifloxacin Monotherapy

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INTRODUCTION

Traditionally, antibacterial agents have been considered to have no significant therapeutic effect against fungal pathogens. In fact, antibacterial agents are routinely used to supplement fungal culture media to enhance recovery of fungi. In the past, reports of cure of fungal keratitis by antibiotic therapy have been rare^{1, 2}. In recent years, however, a number of cases of *Fusarium* keratitis have been reported to have responded to topical antibiotic therapy^{3–5}.

This report describes five cases of fungal keratitis cured with single agent therapy with topical moxifloxacin 0.5%.

CASE REPORTS

CASE 1

A 49 year old male was referred with a 15 day history of foreign body sensation OS that developed while he was working in the yard.

Visual acuity was 20/25. There was a 1.5 mm dense anterior stromal infiltrate in the inferotemporal quadrant. Routine and fungal cultures were obtained and the patient was treated with moxifloxacin 0.5%, one drop every hour pending culture results. Monotherapy with a fluoroquinolone agent was initially utilized because the infiltrate was small and the course had been indolent. The patient did not keep his next appointment. On day 3, mould was identified in the culture. The patient was contacted and finally returned 5 days after the first visit. By the time of his return visit, he was much improved. The pain had resolved and the infiltrate was less dense. Moxifloxacin therapy was continued and the infection resolved over 2 weeks. The organism was identified as *Curvularia spp.* No other organisms were isolated. Final visual acuity was 20/20.

CASE 2

A 52 year old male presented with a 2 day history of severe pain of the left eye. He had experienced a metallic foreign body injury 3 weeks previously, with persistent foreign-body sensation that had worsened. Visual acuity was 20/30. A 2 mm irregularly shaped anterior stromal infiltrate with an overlying epithelial defect was present in the mid periphery at 3 o'clock. There was little surrounding inflammation. The appearance was suggestive of an indolent organism such as fungus. Routine and fungal cultures were taken and Moxifloxacin

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0.5%, one drop every half-hour was prescribed pending culture results. The fluoroquinolone was selected based on experience with case 1.

One day later, the infiltrate had begun to epithelialize and pain had decreased. By day 5, the infiltrate had decreased in area and density. The culture was reported to be positive for mould. Because the patient was doing well, treatment was continued with close follow-up. The infection resolved over the next 2 weeks. Final visual acuity was 20/20. The mould was identified as *Curvularia spp.* No other organisms were isolated.

CASE 3

A 79 year old male with non-insulin dependent diabetes mellitus and a history of 3 previous penetrating keratoplasties in the left eye, originally for the indication of bullous keratopathy, was referred with a one month history of gradually worsening pain. The patient had seen his local ophthalmologist one day previously. At the time of his initial visit he was using no topical medication OS.

Visual acuity was count fingers at 4 feet. The left cornea had an edematous graft with a 4 mm diameter arcuate anterior stromal infiltrate, with finger-like spokes, many of which had a slightly crystalline appearance, extending into the surrounding stroma {Figure 1}.

Cultures were taken and he was initially treated with ceftazidime 50 mg/ml one drop every hour pending culture results. On day 3 cultures grew yeast. At that time, the patient had no significant improvement. A prescription for natamycin was given but the patient stated that he could not afford the medication. He was directed to go to the county general hospital to obtain the natamycin. In the meantime, a sample of moxifloxacin 0.5% was given to be used one drop every hour.

The patient returned 3 days later, having never obtained the natamycin. He stated that he was feeling more comfortable. The infiltrate had begun to respond. The moxifloxacin 0.5% was continued. By the 3rd week of treatment, the infiltrate had resolved. The yeast was identified as *Candida parapsilosis*. No other organisms were isolated.

CASE 4

A 40 year-old female daily wear soft contact lens wearer developed a one week history of increasing pain OD. She was seen by her local ophthalmologist and treated with tobramycin 14 mg/ml and gatifloxacin 0.3%, each one drop every hour, and referred after 2 days with no improvement.

Visual acuity was 20/60 OD. A 1.8 mm anterior stromal infiltrate was present near the visual axis. There were numerous small satellite infiltrates radiating from the central infiltrate {Figure 2}. Routine and fungal cultures were taken and the patient was treated with moxifloxacin 0.5% one drop every half hour pending culture results.

After one day the infiltrate had improved and the pain was decreased. After 3 days, growth of mould was noted. The patient continued to improve, so moxifloxacin 0.5% was continued. After 2 weeks, the infiltrate was inactive-appearing. The moxifloxacin 0.5% was tapered and discontinued over an additional 2 weeks. The mould was identified as *Paecilomyces lilacinum*. No other organisms were isolated.

CASE 5

A 21 year old male was referred with an infiltrate of the right eye. He had a history of soft contact lens wear and had used a “no rub” contact lens solution. He had been under treatment for microbial keratitis for three weeks with gradual worsening. At the time of his

initial visit, he was using ceftazidime 50 mg/ml and vancomycin 25 mg/ml, one drop every half hour. A culture performed two weeks previously had shown no growth.

Visual acuity was 200 E at 6 feet. Slit-lamp evaluation revealed a white, chalky plaque measuring 7.5 mm by 3 mm covering the inferior cornea. A stromal infiltrate was present beneath the plaque {Figure 3}. Finger-like projections extended into the surrounding stroma. Routine and fungal cultures were taken and the patient was initially treated with moxifloxacin 0.5% solution, one drop every half hour pending culture results.

By day 4, when cultures grew mould, the infiltrate was less dense and the edges were more sharply demarcated. The pain had decreased and visual acuity had improved to 20/400. Because the patient was improving, moxifloxacin 0.5% was continued with close follow-up. The moxifloxacin 0.5% was tapered to discontinuation over 6 weeks, during the course of which the plaque sloughed off. Final visual acuity was 20/50 with spectacle correction. The fungus was identified as *Aspergillus flavus*. No other organisms were isolated.

DISCUSSION

Antibiotics that have been reported to have antifungal efficacy are primarily aminoglycoside and fluoroquinolone agents. In 1975, Forster and associates¹ reported that two patients from their series of 16 subjects with corneal-culture-proven fungal keratitis were cured with topical gentamicin therapy. The etiologic agents were *Curvularia pallescens* and *Dreschlera halodes*. The one patient for whom follow-up was available achieved best corrected visual acuity of 20/50. The authors did not note the severity of the original infection.

In 2000, Chodosh and co-authors² reported cure of *Fusarium oxysporum* keratitis with topical tobramycin 14 mg/ml and vancomycin 50 mg/ml. The visual acuity improved from hand motions to 20/30. *In vitro*, the isolate was inhibited by tobramycin at a concentration of 0.45 mg/ml and higher, but vancomycin had no inhibitory effect.

More recently, Munir and associates⁴ reported 5 cases of fungal keratitis responsive to antibiotic therapy. Two cases were cured with moxifloxacin monotherapy. However, both cases were corneal culture negative. In one case, *Bipolaris* species was isolated from the contact lens case and the confocal microscopy was positive for hyphae. In the second case, the contact lens case grew a *Fusarium* species. It was not noted as to whether confocal microscopy was performed on this case. A third patient had corneal culture positive for *Staphylococcus epidermidis* and *Lactobacillus* species. The contact lens culture grew both types of bacteria plus *Fusarium*. The patient was cured with gatifloxacin 0.3% monotherapy. Of the two patients who had positive corneal cultures, both cultures grew *Fusarium*. In one case, the patient was cured by therapy with tobramycin 14 mg/ml and cefazolin 50 mg/ml, while the second patient initially responded to moxifloxacin but relapsed and required natamycin to effect a cure.

In 2007, Rao and co-authors⁵ described 12 patients in Hong Kong with *Fusarium* keratitis associated with the use of ReNu Moisture Loc contact lens solution. Four patients, all of whom had positive corneal cultures, were reported to have been cured with a combination of antibiotics consisting of fluoroquinolones (levofloxacin or ofloxacin), tobramycin, and vancomycin. More recently, Khor and associates³ described 68 eyes of 66 patients in Singapore with *Fusarium* keratitis, observed between March 2005 and May 2006. All had fungus isolated from the cornea. In 11 eyes, (16.2%) topical antibiotic therapy, “typically fortified cefazolin 50 mg/ml and gentamicin 14 mg/ml” led to resolution of the infection.

The antibacterial activity of fluoroquinolone agents is due largely to their inhibitory effect on bacterial topoisomerase⁶. Many fungal pathogens have been noted to have high levels of

topoisomerase^{7, 8} and it has been noted that quinolones are capable of binding fungal topoisomerase^{7, 8}, suggesting a mechanism of potential antifungal effect. In a study of 21 ocular isolates of *Candida*, Ozdek and co-workers⁹ found that both moxifloxacin and gatifloxacin demonstrated antifungal activity. At undiluted concentrations, > 99.9% of growth was inhibited at day one by both drugs. There was no significant difference between the two drugs at full concentration. However, at diluted concentrations, gatifloxacin demonstrated more effect than moxifloxacin.

Day and associates¹⁰ tested the activity of amoxicillin, cefazolin, chloramphenicol, moxifloxacin, tobramycin, and benzalkonium chloride against ocular isolates of *Fusarium spp* and *Aspergillus flavus*. Ten isolates of each organism were tested. The MIC₉₀ of tobramycin and moxifloxacin against *Fusarium* was 700 µg/ml and 2000 µg/ml respectively. The drugs did not inhibit *Aspergillus*. The MIC₉₀ of chloramphenicol for *Fusarium* was 2000 µg/ml, and 4000 µg/ml for *Aspergillus*. The other antibiotics demonstrated no antifungal activity. In contrast, the MIC₉₀ of benzalkonium chloride for *Fusarium* and *Aspergillus* was 64 µg/ml and 16 µg/ml respectively.

Other investigators have studied the interaction of quinolone and antifungal agents. Stergiopoulou and co-authors¹¹ demonstrated that ciprofloxacin, which had no intrinsic antifungal activity, had significant interaction with antifungal agents to potentiate their activity against *C. albicans* and *A. fumigatus*. Other investigators found variable interactions. Nakajima and co-workers¹² demonstrated that DU-6859a, an investigational fluoroquinolone agent, enhanced the *in vitro* antifungal activity of amphotericin B (AmB) against *Candida albicans*, *Candida tropicalis*, *Candida krusei*, *Candida glabrata*, and *Cryptococcus neoformans*; by itself it had no antifungal activity. However, for *Aspergillus fumigatus* the effect varied with the medium, with antagonistic interactions found in RPMI 1640. In animal studies, the agents prolonged survival of mice infected with *C. albicans*, when administered in combination with AmB. Other authors have demonstrated concentration-dependent interactions with additive effect in some cases and antagonism in others^{13, 14}.

In the present series, five patients with fungal keratitis documented by positive corneal cultures had resolution of infection with moxifloxacin 0.5% monotherapy. The organisms killed include *Curvularia spp*, *Aspergillus flavus*, *Candida parapsilosis*, and *Paecilomyces lilacinum*. These cases expand the potential anti-fungal spectrum of fluoroquinolone agents.

These cases are reported to suggest that further studies to identify ways in which fluoroquinolone drugs may be used to enhance antifungal therapy may be productive. However, extreme caution should be utilized in the interpretation of the clinical implications. The experience of Khor and associates³ who found in their large series that only 16% of their cases responded to antibiotic therapy suggests that the vast majority of patients with fungal keratitis require specific antifungal therapy to obtain a favorable outcome.

The current cases were managed prior to the availability of confocal microscopy at our institution. Smears were either negative (3/5) or not obtained (2/5). In two cases the clinical history and appearance were compatible with bacterial keratitis. In three cases, features suggestive of fungal keratitis were present, but moxifloxacin therapy was begun while awaiting culture results because empirical anti-fungal therapy is not recommended. While it is our routine to initiate “fortified” antibiotic therapy for moderate to severe bacterial keratitis, monotherapy with a fluoroquinolone may be utilized pending identification of the pathogen for indolent or small infiltrates, or, based on clinical experience, for infiltrate with features suggestive of fungal infection.

The current cases suggest that initial improvement on antibiotic therapy should not lead to the assumption that the patient has bacterial keratitis. Close follow up should be maintained and one should be aware of the possibility that the patient may have a partially responsive fungal keratitis that may ultimately be inadequately treated by antibiotics alone. In general, corticosteroid therapy should be withheld until the infecting organism has been identified.

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Figure 1. Slit lamp photograph of patient 3. *Candida parapsilosis* keratitis in a corneal graft, with an arcuate infiltrate with finger-like spokes, many of which had a slightly crystalline appearance.

Figure 2.
Slit lamp photograph of patient 4. *Paecilomyces lilacinum* keratitis presenting as a multifocal anterior stromal infiltrate.

Figure 3. Slit lamp photograph of patient 5. *Aspergillus flavus* keratitis at presentation; stromal infiltrate with finger-like projection is present beneath a chalky plaque (A). The infection resolved, leaving a vascularized scar (B)