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Mycotic corneal ulcers caused by *Fusarium* spp. – available therapeutic option

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ABSTRACT

Fungal corneal ulcers caused by *Fusarium* spp. are known as sight threatening infection with bad course.

Fungus properties, diagnostic difficulties and limited therapeutic ways result in poor outcomes.

Three of antimycotic drugs are effective against *Fusarium* spp.: natamycin, amphotericin B and voriconazole. Natamycin is the only drug approved by FDA (Food and Drug Administration) for treatment of corneal ulcers caused by *Fusarium* spp.

Fungistatic work and limited ocular penetration of antimycotic drugs lead to therapeutic keratoplasty in cases with extremely bad course. Patient with recurrent infections and very advanced inflammation, require enucleation.

Currently there is no gold standard way of therapy for *Fusarium* spp. corneal ulcers.

KEY WORDS: corneal ulcer, *Fusarium* spp, natamycin, voriconazole, therapeutic penetrating keratoplasty.

The genus name *Fusarium* was first introduced into the world literature by H. F. Link in 1809. *Fusarium fungi* are commonly found in soil, where they live as saprophytes. As parasites, they often infest economically important plants, i.e. cereals, maize, and potatoes. *Fusarium fungi* are currently considered to be among the most phytotoxic microorganisms in the world. In addition, they are classified as ubiquitous organisms, i.e. those that adapt well to changing weather and soil conditions, and spread more easily with rainfall and air currents [1]. *Fusarium* fungi may be present on the surface of human skin. In immunocompromised patients, especially with granulocytopenia or impaired neutrophil function, they cause invasive opportunistic infections.

Corneal fusarioses are severe, vision-threatening ocular infections which occur typically in tropical climates, in developing countries, where they account for about half of all cases of infectious keratitis [2]. They are most often associated with damage to corneal integrity by the plant agent – the primary habitat of the fungus. Aside from endemic cases, corneal fusarioses also occur in developed countries, representing 1-5% cases of infectious keratitis. The use of soft contact lenses is recognized as the most common risk factor for the development of the condition [2]. Poor outcomes associated with corneal ulcers caused by *Fusarium* spp. can be attributed to diagnostic difficulties, among other factors.

The gold standard in the diagnosis of fungal corneal infections is the culture of scrapings obtained from the ulcer base and margin. As the sample size is very small, inoculation on appropriate media should be performed immediately after taking the sample. The main advantage of this diagnostic method is that it is suitable for evaluating drug susceptibility of the isolated strain. It is important to note, though, that fungal drug susceptibility tests performed *in vitro* may not translate into drug efficacy *in vivo*. In addition, fungi are characterized by slow growth rates on culture media. Consequently, a long waiting time for the test result necessitates prolonged use of empirical treatment based on the initial clinical diagnosis. According to the data reported in the literature, the proportion of positive cultures of corneal scrapings in ulcers of fungal etiology is 52.4% [3]. An important factor in mycological diagnostic work-up is microscopic evaluation of clinical specimens. In many cases, it speeds up the diagnosis of fungal infection and may help in the initial identification of the caus-

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ative fungus. The distinctive shape of *Fusarium* micro- and macroconidia allows for an early start of therapy with appropriate antifungal drugs. In addition to positive culture results, the diagnosis of fusariosis can be corroborated by histopathological findings. A characteristic histopathological feature of fusariosis shown by the Grocott stain is the presence of numerous branching fungal hyphae. Colonies of the *F. solani fungus* on agar media are shown in Figure 1.

In addition, fungal infections often prove unamenable to therapy, as fungi are highly resistant to antifungal drugs, which are characterized by poor penetration into ocular tissues [3]. Fungi of the genus *Fusarium*, similarly to all filamentous fungi, have an ability to produce spore forms and endospores, release drug-protective enzymes, and adapt rapidly to changing conditions, which is how they acquire resistance to drugs. Difficulties associated with the treatment of fungal infections are due to the similarity of the pathogen to human cells. Fungi are eukaryotic organisms, so antifungal drugs typically fail to act selectively only on the pathogen.

Treatment outcomes also depend on the species of the causative fungus. Data collected to date suggest that the most common etiological factor of corneal ulcers caused by *Fusarium* spp. are strains belonging to the *Fusarium solani* species complex (FSSC):]Germany 87% [4], Tunisia 66% [5], India 75.7% [6], Mexico 80.9% [7], USA 77% [8]. FSSC infections require a significantly longer treatment. In addition, a higher proportion of patients infected with FSSC need therapeutic keratoplasty and, despite treatment efforts, have poorer outcomes when compared with infections caused by other *Fusarium* species [9, 10]. Fusarium solani exhibits naturally reduced susceptibility to amphotericin B. The only effective drug for the treatment of this type of infection is voriconazole.

Modern pharmacology has four basic groups of antifungal drugs [11], with echinocandins being the newest addition to the antifungal arsenal.

Echinocandins are large cyclic peptides linked to a long-chain fatty acid which, by inhibiting the synthesis of (1,3)-β-D-glucan – a component of fungal cell walls, cause cell disintegration. Approved therapeutic agents in this category include caspofungin, micafungin, and anidulafungin. The spectrum of activity of echinocandins comprises species of the genera *Candida* and *Aspergillus*. They show fungicidal activity against *Candida* and fungistatic activity against the genus *Aspergillus*. Echinocandins do not penetrate into the ocular structure. *Fusarium* spp. fungi exhibit a natural resistance to drugs of this group because of reduced levels of (1,3)-β-D-glucan in the cell wall.

Amphotericin B, belonging to the group of polyene macrolides, was introduced into therapeutic use in 1955, and for many years was the only effective antifungal drug available for systemic treatment. The mechanism of action of amphotericin B is based on increasing the permeability of the fungal cell membrane by binding to ergosterol. The drug has a broad spectrum of fungicidal activity, including *Candida albicans*, *Cryptococcus neoformans*, *Histoplasma capsulatum*, and *Aspergillus fumigatus*. The activity of the drug towards *Fusarium* spp. varies depending on the isolated strain. Amphotericin B has been shown to produce the strongest inhibitory effect on the growth of *Fusarium* species *in vitro*, with MIC (minimal inhibitory concentration) of approximately 2 mg/l [4, 9, 10]. However, it is not the drug of first choice for the treatment of infections attributed to this etiology because of its high toxicity, low oral bioavailability, and poor tissue penetration (also into the ocular structures) after intravenous administration. Nevertheless, it is used as a rescue drug in patients with refractory fungal infections with a severe, life-threatening course. In ophthalmology, amphotericin B is administered in the form of intracameral injections in the treatment of severe infections spreading into the eyeball [12].

Natamycin is another polyene compound, obtained from Streptomyces cultures. It is as yet the only drug approved by the Food and Drug Administration (FDA) (1960) for topical use in patients with fungal keratitis [13]. The drug's antifungal activity against *Fusarium* spp. is attributable to its interaction with ergosterol in fungal cells. According to various data,

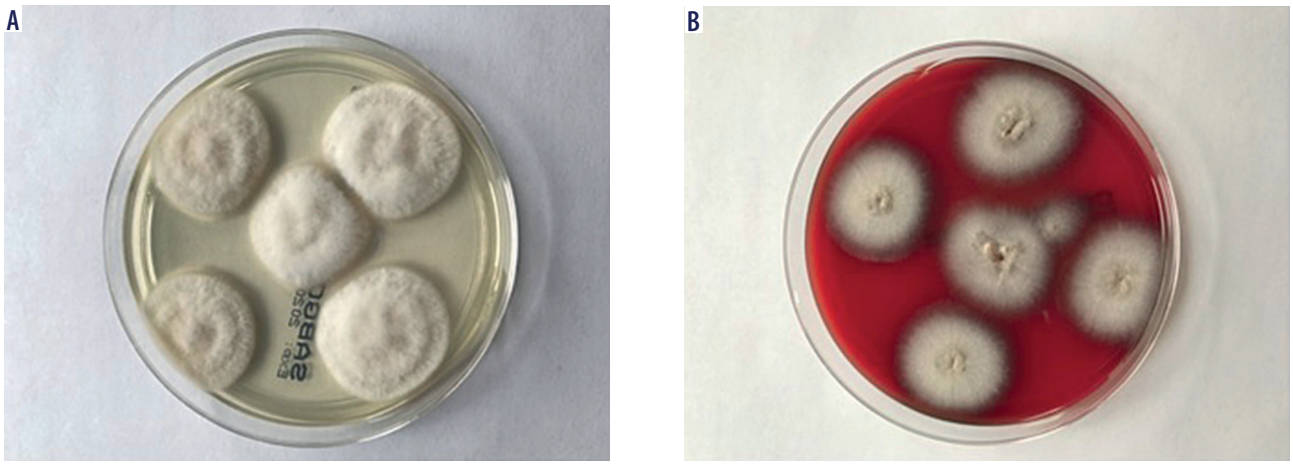

Figure 1. *F. solani* cultured on: A) Sabouraud dextrose agar, B) Columbia agar

the potential of natamycin to inhibit fungal growth in vitro is lower than that of amphotericin B, with MIC in the range of 2.4–8 mg/l [4, 9]. However, since natamycin is characterized by small particle size and excellent penetration through the cornea after topical administration, its efficacy in the treatment of ocular infections caused by *Fusarium* spp. is superior to that of amphotericin B [4, 14]. The only available dosage form of the drug is natamycin 5% eye drops. The drug is well tolerated, and possible adverse effects after application are limited to mild irritation symptoms [4, 11]. The drug is not completely absorbed after oral administration.

Natamycin 5% eye drops are recommended for the treatment of fungal keratitis caused by *Fusarium* spp. as a suggested primary therapeutic regimen [15]. In Poland, natamycin 5% eye drops are not available, and treatment is only possible after obtaining the drug under the direct imports procedure.

Azoles are a group of antifungal agents with a broad spectrum of activity, high oral bioavailability, and relatively low toxicity [11, 13]. Their antifungal properties are due to the inhibition of lanosterol demethylase, one of the fungal cytP450 enzymes. The process inhibits ergosterol synthesis and consequently disrupts the fungal cell membrane. However, the effect produced by azoles on cytP450 leads to a range of interactions between drugs of this group with other drugs metabolized via cytP450 enzymes, and modifies the synthesis of human steroid hormones. Based on structural differences, the group of azoles has been divided into two subgroups: imidazoles and triazoles. Triazole derivatives are characterized by more selective activity, less effect on the biosynthesis of steroid hormones in humans, and superior bioavailability and tissue penetration after oral administration, which is why they are viewed as safer than imidazole derivatives. Triazoles include fluconazole, itraconazole, and voriconazole. The spectrum of activity of selected triazoles is shown in Table I.

The synthesis of DNA and RNA in fungal cells can be inhibited by flucytosine, belonging to the group of antimetabolites. It is a prodrug that is biotransformed into 5-fluorouracil [16]. Flucytosine is well absorbed after oral administration and exhibits high bioavailability to tissues. It is known to have antifungal activity against *Candida* spp. and *Cryptococcus* spp. [11]. The disadvantage of the drug is that, when used in monotherapy, it rapidly leads to the emergence of fungal resistance. Consequently, in the treatment of endophthalmitis flucytosine is used in combination with another drug, for example amphotericin B [15].

Table I. Species-dependent activities of some triazoles

Fungal species	Voriconazole	Itraconazole	Fluconazole
Candida spp.	+	+	+
C. neoformans	+	+	+
H. capsulatum	+ (*in vitro*)	+	+
Aspergillus spp.	+	+	–
Fusarium spp.	+	–	–

Multiple studies have been conducted to establish a uniform patient management protocol for fungal corneal ulcers caused by *Fusarium* spp. by comparing the efficacy of available antifungal agents, but no gold standard has yet been established [10, 17].

One such study was a randomized, double-blind, multicenter, controlled trial conducted in India with the objective to compare the efficacy of a topically applied voriconazole formulation and topically applied natamycin in the treatment of fungal corneal ulcers [18]. A total of 323 patients with diagnosed fungal corneal ulcers caused by filamentous fungi were enrolled. The causative organisms included *Fusarium* spp. (128 patients), Aspergillus spp. (54 patients), and other species of filamentous fungi (141 patients). The primary outcome of the study was best-corrected visual acuity (BCVA) after three months of treatment. The secondary endpoints included the size of corneal infiltrate or scar formed after three weeks and three months, the presence of fungal cells in the evaluated material after six days of treatment, and the proportion of patients who had corneal perforation or required therapeutic keratoplasty. After three months, the BCVA in patients receiving voriconazole was 1.8 times inferior to that in the natamycin group. There was no difference between the size of infiltrate or scar formed after three months of treatment between the two study groups. The proportion of positive cultures after six days of treatment was higher in the voriconazole-treated group. The differences were more pronounced when the population with ulcers caused by *Fusarium* spp. was isolated from the study groups. Of these patients, the BCVA in the natamycin-treated group was 4.1 times better than in the voriconazole-treated group, while the areas of scarring after three months of treatment were significantly smaller in the natamycin-treated group. The proportion of positive cultures after six days of treatment was significantly lower in the natamycin group. In addition, a significantly higher rate of corneal perforation was observed in the voriconazole-treated population, leading to withdrawal from the study.

The findings obtained in subsequent studies were consistent with the above observations, confirming the superiority of topically applied natamycin over the topically applied voriconazole formulation in fungal ulcers of the cornea caused by *Fusarium* spp. [19].

A systematic Cochrane Review (2015) evaluated the efficacy of eight drugs used for the treatment of fungal corneal ulcers: voriconazole, econazole, itraconazole, miconazole, natamycin, amphotericin B, chlorhexidine, and sulfadiazine. An analysis of pooled data showed that patients with fungal corneal ulcers treated with the topical natamycin formulation are at a lower risk of corneal perforation and achieve better BCVA results compared to the patients treated with the other formulations listed above [20].

Another randomized, double-blind, controlled trial involving patients with fungal corneal ulcers analyzed the benefits of adding an oral formulation of voriconazole to a topically applied formulation of natamycin and voriconazole [21]. The study enrolled 240 patients with severe fungal corneal

ulcers who were divided into two groups: one received oral voriconazole at a saturating dose of 2 × 400 mg followed by 2 × 200 mg for 20 days, while the other group received a placebo. The primary endpoint of the study was the corneal perforation rate determined at three months. The secondary endpoints included the proportion of positive cultures after six days of treatment, BCVA at three weeks and three months, size of the infiltrate or area of scarring at three weeks and three months, and rate of adverse effects associated with the use of the oral voriconazole formulation. The first analysis of study results revealed no significant differences in the evaluated parameters between the study group and the control group, except for an increased proportion of adverse effects manifested as elevated levels of liver enzymes and visual hallucinations in the group receiving oral voriconazole. A follow-up analysis of study results after isolating the populations with corneal ulcers caused by *Fusarium* spp. and corneal ulcers brought on by other causative agents showed that adding oral voriconazole to topical medications may be beneficial for the treatment of infections caused by *Fusarium* spp. In the population with *Fusarium* spp. infection, the group receiving oral voriconazole had a lower rate of corneal perforations and smaller areas of scarring at three months of therapy. However, there was no difference in BCVA between the study group and the control group [22].

In a recently published study, Guo et al. demonstrated a synergistic activity in vitro of the combined use of natamycin and azithromycin against FSSC strains [23].

In fungal corneal ulcers characterized by poor response to topical and systemic treatments, intracameral injections of amphotericin B have been shown to shorten the time to resolution of hypopyon in the anterior chamber, improve BCVA scores, and reduce the duration of active infection [24, 25].

There have been reports highlighting the benefits of voriconazole injections into corneal stroma as an adjuvant therapy in refractory corneal ulcers of fungal etiology [26, 27], but ulcers caused by *Fusarium* spp. have a poorer response to the administered drug compared to other fungal organisms [28].

In addition to pharmacotherapy, attempts have been made to treat fungal keratitis by applying the technique of cross-linking (CXL) to harden the corneal tissue. The antifungal activity of this therapeutic modality has been attributed to the biocidal properties of UV-A radiation enhanced by the riboflavin chromophore. However, a randomized controlled trial conducted in a group of patients with microscopically confirmed moderate fungal corneal ulcers failed to demonstrate any benefits of CXL as an adjuvant therapy added to topical natamycin or voriconazole treatment. Furthermore, it was found that the group of patients additionally receiving CXL had worse BCVA results during the three-month follow-up [29]. Nevertheless, there are also reports suggesting that CXL may produce a beneficial therapeutic effect in the management of early superficial fungal corneal ulcers [30].

In cases where the infection progresses despite intensive conservative treatment, therapeutic keratoplasty is required. The main goal of the procedure is to eradicate the pathogen. According to the literature data, the rate of recurrence of infection is 5-14% [31, 32]. Common postoperative complications include graft decompensation and postoperative increase in intraocular pressure. A retrospective study conducted in an Indian population showed that 11.9% of patients with fungal corneal ulcer ultimately required therapeutic keratoplasty despite undergoing conservative treatment [33]. In the same study, it was observed that during the early postoperative period after therapeutic penetrating keratoplasty (TPK), complete eradication of the fungus was achieved in 89.9% of cases. A total of 10.1% of patients presented with a recurrence of infection within 15 ±9.3 days after surgery. At one-year follow-up, 12.3% of corneal grafts retained clarity, achieving a mean BCVA of 20/40. The authors of the study emphasize that the lower proportion of successful grafts compared to that reported in other studies may be due to the poor quality of material harvested for the procedure (endothelial cell density of 1500-2000 cells) and the need to use larger grafts because of advanced inflammatory infiltration. *Fusarium* spp. was shown to be the causative agent in 15.7% of the cases [33].

A similar retrospective study, also evaluating the effects of TPK in the treatment of severe advanced fungal corneal ulcers, showed 79.6% of clear corneal grafts at two-year follow-up. In the study population, *Fusarium* spp. infection was confirmed in 65% of patients [34]. Another retrospective study, conducted at the University of Iowa (USA), shows that 43.8% of patients treated for fungal corneal ulcer required keratoplasty following failure of prior treatment, and therapeutic success defined as complete eradication and maintenance of clear graft was achieved in 53.1% of patients during a two-year follow-up period. *Fusarium* spp. infection was confirmed in 34.4% of patients in the study population [35]. The above findings show that therapeutic keratoplasty has a limited success rate in the treatment of fungal corneal ulcers. Despite the procedure, antifungal therapy must be continued, and long-term outcomes after surgery are uncertain. A possible alternative to TPK is therapeutic deep anterior lamellar keratoplasty (TDALK). In a retrospective study, the effects of TPK and TDALK performed in a group of 126 patients with infectious keratitis of bacterial, fungal or protozoal etiology, refractory to conservative treatment, were compared. According to the data from this study, pathogen eradication was achieved in 88% of patients undergoing TPK and 84.6% of patients treated by TDALK. In addition, the TDALK-treated group achieved a better improvement in visual acuity, by approximately 2 lines, compared with the TPK-treated group, and had better graft survival at one-year follow-up (90% after TDALK, 78.4% after TPK) [36].

However, if all corneal layers are affected and an inflammatory response is seen in the anterior chamber, the only appropriate therapeutic approach is a penetrating graft. The area of the eyeball where hyphae are present is considerably larger than the visible infiltrate in the stroma of the cornea.

Despite intensive conservative treatment and surgical management, in 23% of cases the severity of the infection is such that the patient needs eye removal surgery [4].

CONCLUSIONS

Fungal keratitis caused by *Fusarium* spp. has been a challenge in ophthalmology for many years because of diagnostic difficulties and limited therapeutic possibilities. There is as yet no gold standard for patient management. In cases where corneal ulcer is suspected to be caused by *Fusarium* spp. combination therapy with topical and systemic antifungal agents is initiated. Also, such patients frequently require surgical intervention. Among the topical agents, natamycin 5% has a proven efficacy and established safety profile in the treatment of corneal ulcers induced by *Fusarium* spp. However, the use of the drug in clinical practice is limited by its unavailability on the Polish market. Topical voriconazole formulations – despite their broad spectrum of activity – are not recommended for monotherapy of corneal ulcers caused by *Fusarium* spp. because of proven high incidence of corneal perforations during treatment. In view of the fungistatic activity of most available antifungal agents, rapid progression of infection, and penetration of ocular structures by fungal hyphae, corneal ulcers caused by filamentous fungi of the genus *Fusarium* are associated with poor treatment outcomes despite the use of available therapeutic interventions. Mycological diagnostic work-up with the evaluation of characteristic fungal structures in microscopic slides reduces the time before appropriate antifungal therapy can be initiated.

DISCLOSURE

The authors declare no conflict of interest.

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