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CLINICAL AND EPIDEMIOLOGICAL STUDY

The efficacy of voriconazole in 24 ocular *Fusarium* infections

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Abstract
Purpose We examined, retrospectively, the efficacy of voriconazole in *Fusarium* eye infections.
Methods Voriconazole-treated patients with proven or probable keratitis or endophthalmitis from the voriconazole database (9 patients) and six French ophthalmology departments (15 patients) were included. Sociodemographic features, predisposing factors, history of corneal trauma, associated ocular conditions, other diseases and prior therapies were analysed. Investigator-determined success was defined as infection resolution with medical treatment. Failure was no response or persistent infection and required surgery.
Results Most patients were Caucasian (83 %) and male (71 %). The infection was keratitis (63 %) or endophthalmitis (37 %) and proven in 23 (96 %). Prior therapy included topical and/or systemic amphotericin (46 %), fluconazole (17 %) or others (33 %), often in combination. Causative fungi were *Fusarium solani* (14, 58 %), *Fusarium moniliforme* (1), *Fusarium oxysporum* (1) and *Fusarium* spp. (8). Voriconazole was administered systemically, topically and/or by intraocular injection, and 16 patients (67 %) received salvage and eight primary therapy. The overall response was 67 % (73 % keratitis and 56 % endophthalmitis) but seven patients required adjunctive surgery. However, response was 63 % for eight primary therapy patients and 69 % for 16 salvage therapy patients. Response by species was *Fusarium solani* 64 % (9/14) and all others 80 % (8/10). In 13 patients (77 %), voriconazole was used in combination (response 69 vs. 64 % alone) with topical [amphotericin B 10/24 (42 %), caspofungin 5 (21 %), natamycin 1 (4 %)] and systemic agents [caspofungin 3 (13 %), amphotericin 2 (8 %)].
Conclusions Topical and systemic voriconazole appears to be effective alone or in combination with other agents for treating severe *Fusarium* keratitis or endophthalmitis.

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Introduction

Keratitis and endophthalmitis are sight-threatening infections, with keratitis being especially prevalent in outdoor workers in the tropics and subtropics [1]. The incidence of keratitis has also increased over the last few years [2]. Fungal eye infections occur less frequently in temperate countries but remain devastating. They may also be associated with the dissemination of fungal infection from other body sites, mostly in immunocompromised hosts [3–5].

Voriconazole is generally well tolerated in humans after topical instillation to the cornea [6] or intracameral injection [7], and voriconazole eye drops and systemic applications have been shown to penetrate into the aqueous and vitreous humours, attaining potentially therapeutic concentrations [8–10]. The effectiveness of voriconazole in treating fungal eye infections has also been reviewed [11, 12] and there are an increasing number of clinical studies [13, 14] and case reports of the use of voriconazole for treating both fungal keratitis (e.g. [15–17]) and endophthalmitis (e.g. [18–20]). Voriconazole may also be effective against eye infections caused by some free-living amoebae, such as *Acanthamoeba* and *Naegleria fowleri* [21–23]. However, voriconazole is known to cause visual disturbances after systemic administration [24, 25], and its advantages as a topical therapy for keratitis compared with natamycin have been questioned [14, 26].

Fusarium spp., particularly *Fusarium solani*, are frequent causative agents of keratitis, as well as exogenous or endogenous endophthalmitis [3]. Recently, outbreaks of *Fusarium* spp. keratitis have been reported in contact lens wearers [27–29]. *Fusarium* infections can also be difficult to treat due to their poor susceptibility to most antifungal agents [3]. However, voriconazole has been shown to be effective for the management of systemic *Fusarium* infections in immunocompromised hosts [30, 31] and in various case studies of *Fusarium* eye infections [32].

We report the results of an international, retrospective study of the efficacy of voriconazole in 24 patients with *Fusarium* keratitis or endophthalmitis.

Materials and methods

Patients

The Pfizer voriconazole clinical database was queried for ocular *Fusarium* infections from 1996 until 2002. These patients came from clinical studies approved by ethics committees and conducted in accordance with the Declaration of Helsinki. In addition, ocular *Fusarium* infections notified at the French National Reference Centre for Mycoses and Antifungals (NRCMA), Institut Pasteur, Paris, France, from June 2002 to January 2009 were identified and data for each patient who presented with culture-proven *Fusarium* eye infection and who were treated with topical and/or systemic voriconazole were collected.

The included cases were queried on sociodemographic features, predisposing factors, history of corneal trauma, associated ocular conditions such as the presence of contact lenses, other systemic diseases and therapy received prior to presentation. All the cases were reviewed by three of the authors (P.T., G.O., O.L.).

Clinical procedures

A clinical examination was performed on each patient by an ophthalmologist using a slit lamp. *Fusarium* eye infections were separated into two groups: fungal keratitis and fungal endophthalmitis. Clinical features were documented and corneal ulcers or infiltrates were recorded.

Microbiological investigations

Laboratory diagnosis was made by means of smear staining and fungal culture. Patients with presumed fungal corneal ulcers underwent corneal sampling. Smear direct microscopic evaluation was performed after staining. The fungal isolation was generally carried out on Sabouraud dextrose agar incubated at 30 °C for up to 14 days. *Fusarium* identification relied on standard phenotypic techniques.

Treatment

The patients were treated with systemic and/or topical voriconazole and, in seven cases, also by intraocular injection.

Topical voriconazole was prepared by appropriate dilution of the voriconazole intravenous solution commercial formulation with saline [33]. The final voriconazole concentration in the eye drops was not controlled across the centres but was usually 1 %. Eye drop administration and duration of use was also not controlled. However, at some centres, eye drops were administered every 15 min during the first hour, then every hour for the following 48 h. The treatment was progressively tapered and/or modified according to the clinical response and the fungal susceptibility testing.

Voriconazole for intraocular injection was prepared by appropriate dilution of the voriconazole iv solution commercial formulation with saline, typically to a final 1 % voriconazole concentration.

Systemic voriconazole was used for proven endophthalmitis or when infection was deep in the cornea, unresponsive to topical antifungal treatment or when extension into the anterior chamber was suspected. Voriconazole was administered at the recommended dosing regimes (6 mg/kg q12 iv on day 1, then 4 mg/kg q12 iv from day 2 onwards, followed by a switch to oral dosing at 200 mg bid po; or 400 mg bid po on day 1, followed by 200 mg bid po from day 2 onwards).

In general, if the status of any corneal ulcers deteriorated or did not improve after 5–7 days of topical and systemic antifungal therapy, surgical interventions were recommended, including therapeutic penetrating keratoplasty or therapeutic lamellar keratoplasty.

Success or failure of therapy was determined by the local investigator.

Results

The 24 patients in this study came from 14 centres in six countries and 9 (38 %) were from the voriconazole database, while the remaining 15 (62 %) were from various French university hospitals. Some 71 % were male, 83 % were Caucasian and they had a median age of 57 years (Table 1).

Table 1 Demographic and clinical data

Demographic	Number (%)
Total patients	24 (100)
Male	17 (71)
Female	7 (29)
Age (years)	Median 57 (range 26–83)
Race	
Caucasian	20 (83)
Other	4 (17)
Clinical data	**Number (%)**
Certainty of infection	
Proven	23 (96)
Probable	1 (4)
Sites of infection	
Keratitis	15 (63)
Endophthalmitis	9 (37)
Underlying conditions	
Surgery	3 (12)
Contact lens wear	8 (33)
Trauma	5 (21)
Steroids	2 (8)
Normal/unknown	6 (25)

Most patients (96 %) had proven disease and suffered from keratitis (63 %), and their infection was frequently a result of some form of localised damage (Table 1).

Fusarium solani was the most common species isolated (58 %), although 33 % of *Fusarium* isolates were not speciated (Table 2). Eight patients (33 %) received no prior therapy, while the type of therapy was unknown in a further three patients. Amphotericin B (mostly topical) was the most common prior therapy used (Table 2).

The overall response rate to voriconazole therapy was 67 % (keratitis 73 % and endophthalmitis 56 %) (Table 3). The eight patients receiving primary voriconazole therapy showed a response rate of 63 %, compared with 69 % for the 16 receiving salvage therapy. Combination therapy of voriconazole with other agents, mostly topical amphotericin B (although nine patients received triple therapy), gave a marginally better response rate (69 %) than voriconazole alone (64 %). Those patients with a confirmed *F. solani* infection (11 with keratitis and three endophthalmitis) showed a worse response rate (57 %) than those with other known species and unspeciated infections (80 %).

The overall median duration of voriconazole therapy was 54 days (range 7–213 days) (Table 4). Patients with keratitis had a shorter median therapy duration and showed a somewhat higher response rate (73 %; median therapy duration 60 days, range 7–213 days) than those with endophthalmitis (56 %; median therapy duration 70 days, range 11–135 days). The best response by underlying condition was shown by the 16 patients (11 with keratitis) with some form of local eye damage (surgery, trauma, contact lens use, burns; 75 %) compared with all others (50 %). Figure 1a, b exemplifies the efficacy of voriconazole in a patient with *Fusarium* keratitis.

Table 2 Pathogens and prior therapy

Clinical data	Number
Fusarium species	*F. solani* complex = 14
	F. moniliforme = 1
	F. oxysporum complex = 1
	Fusarium spp. = 8
Prior therapy	Yes = 13; no/unknown = 11
	Amphotericin B = 11 (topical or parenteral)
	Caspofungin = 1
	Fluconazole = 4
	5-Flucytosine = 2
	Itraconazole = 2
	Miconazole = 1 (topical)
	Natamycin = 1 (topical)
	Polyhexamethylene biguanide = 1 (topical)

Table 3 Clinical outcomes

Response parameter	Clinical response, *n/N* (%)
Overall response rate	16/24 (67)
Keratitis	11/15 (73)
Endophthalmitis	5/9 (56)
Voriconazole primary therapy	5/8 (63)
Voriconazole salvage therapy	11/16 (69)
Voriconazole monotherapy (topical and/or systemic)	7/11 (64)
Voriconazole in combination therapy[a]	9/13 (69)
F. solani group	8/14 (57)
All other *Fusarium* isolates	8/10 (80)

[a] Amphotericin B = 13 patients (topical and/or systemic), caspofungin = 7, itraconazole = 1, natamycin = 1

Table 4 Outcome by underlying condition

Underlying condition (*n* patients)	Response by site, *n/N* (%)		Median voriconazole therapy in days (range)
	Keratitis	Endophthalmitis	
Steroids (2)	0/1 (0)	1/1 (100)	43–110
Surgery, trauma, contact lens use, burns (16)	9/11 (82)	3/5 (60)	47 (7–213)
Immune normal/ unknown (6)	2/3 (66)	1/3 (33)	92 (11–145)
Total (24)	11/15 (73)	5/9 (56)	54 (7–213)

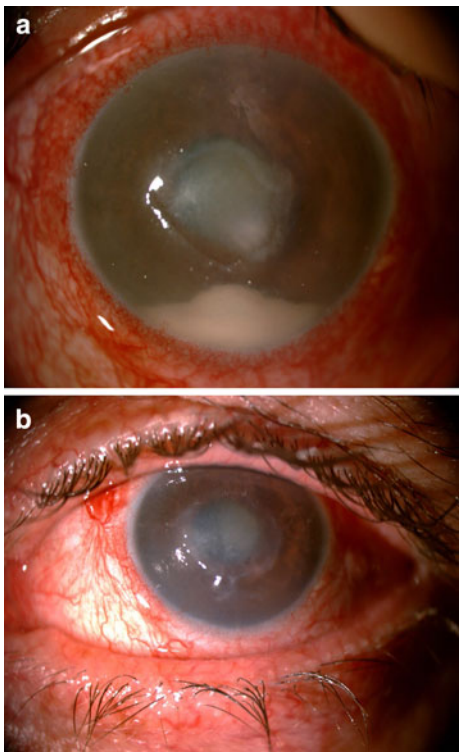

Fig. 1 **a** Patient with *Fusarium* keratomycosis complicated by hypopyon (signs of inflammation in the anterior chamber) prior to voriconazole therapy. **b** Same patient after voriconazole therapy. Visual acuity improved from hand movement only before voriconazole therapy to 20/200 after therapy

Discussion

Fungal keratitis and exogenous or endogenous endophthalmitis are severe ocular infections. Voriconazole has been used for treating patients with keratitis and endophthalmitis since 2000, but has only recently been formally tested in small clinical trials of keratitis [13, 14]. These two trials suggest that topical voriconazole alone may not be more effective than natamycin in keratitis caused by a range of different fungi. However, other literature suggests that it may be a promising therapy for eye infections, especially those refractory to standard antifungal agents [11], including *Fusarium* [32]. Finally, voriconazole has been shown to be effective in five patients with endogenous *Candida* endophthalmitis [34], while in a recent study of 248 candidaemia patients, 29/31 cases with concomitant *Candida* chorioretinitis or endophthalmitis were treated successfully with voriconazole [35].

Therapeutic aqueous and vitreous levels of voriconazole are achieved after either topical or systemic administration [9], and after local application of the diluted intravenous formulation (eye drops, intravitreal or intracameral application), which are apparently well tolerated [10, 36–38]. In addition, Galarreta et al. [39] have demonstrated full or part sensitivity to voriconazole for all 20 of the keratitis isolates they tested, while voriconazole has been shown to have good activity in vitro against clinical isolates of a wide range of filamentous fungi [40].

We do not present susceptibility data for the *Fusarium* isolates in this analysis, although voriconazole minimum inhibitory concentrations (MICs) for isolates from 11 patients in the Pfizer database have been published and range from 1.0 to 16.0 mg/L [40]. The results of the antifungal susceptibility testing of *Fusarium* spp. reveal a wide susceptibility range, with *F. solani* apparently resistant to most antifungals, thus, making such testing of limited value for therapeutic decision-making [41–43]. In our study, patients infected with *F. solani* also responded less effectively to voriconazole therapy than other *Fusarium* species, suggesting that species identification is potentially of more clinical use than the actual MIC. In addition, it should be noted that no in vitro/in vivo correlation has yet been demonstrated for the antifungal management of fusariosis.

Clearly, our study is limited by being small and retrospective in nature, with patients receiving differing dosages

and applications of voriconazole. This complicates interpretation of the results. However, we report an overall response rate of 67 % in the 24 patients, despite the majority having failed prior therapy. Patients with keratitis responded somewhat better than those with endophthalmitis, even though the duration of therapy was longer in the latter group. Patients receiving voriconazole as primary therapy had a similar response rate (63 %) compared with those receiving it as salvage therapy (69 %). All but one of these primary therapy patients received voriconazole combined with topical amphotericin B. Indeed, combination therapy with amphotericin B in keratitis gave an overall response rate of 72 % (8/11) and this may represent the optimum treatment, at least for *Fusarium* keratitis.

In summary, voriconazole appears to be a promising addition to the therapeutic armamentarium for treating *Fusarium* spp. infections of the eye. Prospective clinical trials with defined topical and systemic doses of voriconazole are clearly desirable in order to establish fully its role in treating fungal keratitis and endophthalmitis in general.

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Conflict of interest P. T. was previously an employee of and then a consultant to Pfizer; G.O. none to declare; T.G. none to declare; P.G. none to declare; A.-L.B. none to declare; M. C. none to declare; F. G. has received speaker fees from Schering and MSD; D. P. none to declare; S. R. none to declare; K. S. none to declare; V. B. none to declare; O. L. is a member of the speaker bureaus of Pfizer, MSD, Astellas and Gilead Sciences. Pfizer had no decision-making role in the design, execution, analysis or reporting of this research.

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