Ahmad Dahlan Medical Journal
VOL 6, No. 1, 64-79
http:// http://journal2.uad.ac.id/index.php/admj

Literature Review

Posaconazole for the Treatment of Refractory Keratomycosis: A Systematic Review

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ARTICLE INFO

Article history
Received 09 Mar 25
Revised 13 May 25
Accepted 15 May 25

Keywords:
keratomycosis,
fungal keratitis,
refractory,
posaconazole,
antifungal,

ABSTRACT

Fungal infections such as keratomycosis are one of the most difficult conditions to treat. Approximately half of patients with keratomycosis do not respond to antifungal treatments and carries a higher risk of developing endophthalmitis. If this problem is not treated promptly and effectively, it can lead to vision loss. The use of posaconazole, a newer triazole, for keratomycosis has attracted new interest due to its broad spectrum and good ocular penetration. Therefore, we conducted a systematic review to assess and conclude the efficacy of posaconazole for refractory keratomycosis. We conducted a systematic review according to PRISMA guidelines. A comprehensive search in PubMed, Scopus, ScienceDirect and Google scholar was conducted from the beginning to January 12 2025. Duplicate publications, review articles and incomplete articles were excluded and the quality of the articles were assessed using a standardized tool. The database searches identified a total of 2668 articles. A thorough review of the abstracts and titles led to the exclusion of 1209 items. Finally, we identified 6 articles through full-text reading and analysis, which included 11 patients. All cases reported were successfully treated with posaconazole. In conclusion, posaconazole possibly effective, especially for refractory cases.

INTRODUCTION

Keratomycosis is another name for fungal or mycotic keratitis. It is one of the main causes of visual impairment and is regarded as a sight-threatening condition since it involves fungal or yeast

infections of the cornea.[1] A patient's immunocompromised state, extended consumption of oral antibiotics or corticosteroids, incorrect contact lens use, chronic ocular surface illness, corneal damage from plants or contaminated items, eye procedures, and other factors can all contribute to keratomycosis[2,3,4,5,6]. The dominant pathogen causing keratomycosis is the genus Fusarium, and the second most common pathogen is the genus Aspergillus[7].

In order for proliferative hyphae to deeply penetrate an undamaged Descemet's membrane, filamentous fungi must first penetrate a healthy cornea[8]. Antifungal medications should be administered to patients with keratomycosis as soon as possible[9]. Three kinds of antifungal agents—polyenes, triazoles, and echinocandins—are used for the treatment of fungal infections[10]. Numerous trials have demonstrated the efficacy of well-known medications for keratomycosis, including voriconazole, fluconazole, amphotericin B, and natamycin[11]. Topical amphotericin B and natamycin are the primary treatments for keratomycosis. The only antifungal drug that has received FDA authorization is natamycin[12]. However, there have been cases of keratomycosis that is refractory to these medications[13,14]. Fusarium frequently shows resistance to current antifungal medications. Due to the low corneal penetration of the majority of antifungal medications, some instances do not respond to them[15]. Thus, for deep-seated fungal ulcers, the use of antifungal agents with improved water penetration, like triazoles, has been investigated[16]. Topical natamycin and voriconazole have been suggested as first-line therapies for filamentous keratomycosis in recent years. Prior research has indicated that voriconazole is better for both results[17].

Posaconazole, a newer triazole, has been associated with some encouraging results for treating filamentous keratomycosis when used at a high oral dose[18]. Imidazoles and triazoles are two types of azoles that are utilized as alternate or supplemental treatments in situations that are resistant or non-responding[19]. Posaconazole, one of the newest triazoles, is being utilized more and more to treat keratomycosis. posaconazole, a synthetic structural analogue of itraconazole, has antifungal and yeast properties in vitro, including antimicrobial properties against mucormycosis agents[20]. Keratomycosis has been effectively treated with posaconazole, either alone or in combination with other antifungal medications[21, 22]. In vitro studies comparing posaconazole to six other fungal agents (fluconazole, voriconazole, miconazole, natamycin, amphotericin B, and caspofungin) revealed that posaconazole is highly effective against various fungi that cause keratitis[23]. A high-dose posaconazole that was administered to patients with refractory keratomycosis who did not respond to conventional treatments showed a significant clinical improvement.

Many studies have examined the effectiveness of posaconazole as an alternative antifungal

up to this point, both as an adjuvant and as an initial treatment for keratomycosis. However, a systematic evaluation of its efficacy has not been conducted. In order to evaluate and draw conclusions regarding posaconazole's effectiveness in treating refractory keratomycosis, we carried out a systematic review about it.

METHOD

This study was intended to assess posaconazole's effectiveness in treating refractory keratomycosis. The assessment was conducted in compliance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement standards in order to guarantee an objective approach[24].

SEARCH STRATEGY

This data acquisition was obtained by searching for basic data electronically in PubMed, ScienceDirect, Scopus and Google Scholar. The data search from the beginning to January 12, 2025. One of the reviewers (ARA) stated the development of the data search strategy by using related keywords and referring to medical subject headings (MeSH) such as "keratomycosis" OR "mycotic keratitis" OR "mycotic" OR "fungal keratitis" AND "posaconazole" OR "antifungal agents". The results of this search were then combined and removing the duplicates.

ELIGIBILITY CRITERIA

To assess the eligibility was carried out on the entire study, whose inclusion criteria accompanied patients who diagnosed keratomycosis whose treatment was through posaconazole in any form or without comparison to placebo or other types of antifungal agents. We did not limit whether the article was an RCT, observational study, case report, or case series, but unfortunately the studies we found were limited to case reports and case series. Each of these studies was designed to review studies that were not limited to language, country, and date of publication. In this case there is an exception for patients with mixed infection keratitis who did not have the availability to be included in this article.

Based on its inclusion and exclusion criteria, the PRISMA statement recommendations were followed in the use of the approach in this study. In the process of selected studies and duplications that were removed using Rayyan AI and the review was carried out by ARA (Adelia Rizka Amila) and JAAM (Jamaluddin Ahmad Ali Mas'ud). Then to analyze this text was carried out on the entire study in order to identify the formulation of appropriate problems to be included in this study. NWA (Norita Wahyuniawati Asfiana) also acts as a mediator if there are differences of opinion in

the writing process, which if this happens, then a joint discussion will be held as a solution.

DATA EXTRACTION AND QUALITY ASSESSMENT

For the extraction of this data is held by ARA and JAAM as the authors, which are poured into a table via Google Sheets to extract the data according to this study. If there are differences of opinion between the three authors, then the role of mediator is held by NWA and then a discussion is carried out together. Data extracted were author, study design, region, age, gender, medical history, ocular examinations, interventions, intervention effects and reported findings. Finally, the articles are screened and synthesized into a qualitative systematic review. The JBI (Joanna Briggs Institute) Critical Appraisal Tool was used in this research to assess the quality[25]. Risk assessment was performed by ARA and NWA.

	Yes	No	Unclear	Not applicable
1. Is the review question clearly and explicitly stated?	✓	☐	☐	☐
2. Were the inclusion criteria appropriate for the review question?	✓	☐	☐	☐
3. Was the search strategy appropriate?	✓	☐	☐	☐
4. Were the sources and resources used to search for studies adequate?	✓	☐	☐	☐
5. Were the criteria for appraising studies appropriate?	✓	☐	☐	☐
6. Was critical appraisal conducted by two or more reviewers independently?	✓	☐	☐	☐
7. Were there methods to minimize errors in data extraction?	✓	☐	☐	☐
8. Were the methods used to combine studies appropriate?	✓	☐	☐	☐
9. Was the likelihood of publication bias assessed?	✓	☐	☐	☐
10. Were recommendations for policy and/or practice supported by the reported data?	✓	☐	☐	☐
11. Were the specific directives for new research appropriate?	✓	☐	☐	☐

Overall appraisal: Include ✓ Exclude ☐ Seek further info ☐

Figure 1. JBI Critical Appraisal Tool for quality assessment

RESULTS

A total of 2668 publications (Figure 2) were found using the basic data search in this study. These were then filtered using the inclusion and exclusion criteria specified in the study selection. A thorough review of the abstracts and titles led to the exclusion of 1209 items. Finally, we identified 6 articles through full-text reading and analysis, which included 11 patients.

The result to find the main studies that have been selected is been listed in Table1. Six patients were males (54,54%) and five patients were females (45,45%). The majority of the patients age is less than 50 years old 6 (54,54%). The etiology of the cases mostly come from Fusarium species (54,54%) and most of them have a medical history SCL (63,63%). Almost all of the cases presented with pain (72.72%), worsening vision (36,36%), redness (27.27%) and only two cases others symptoms (18,18%).

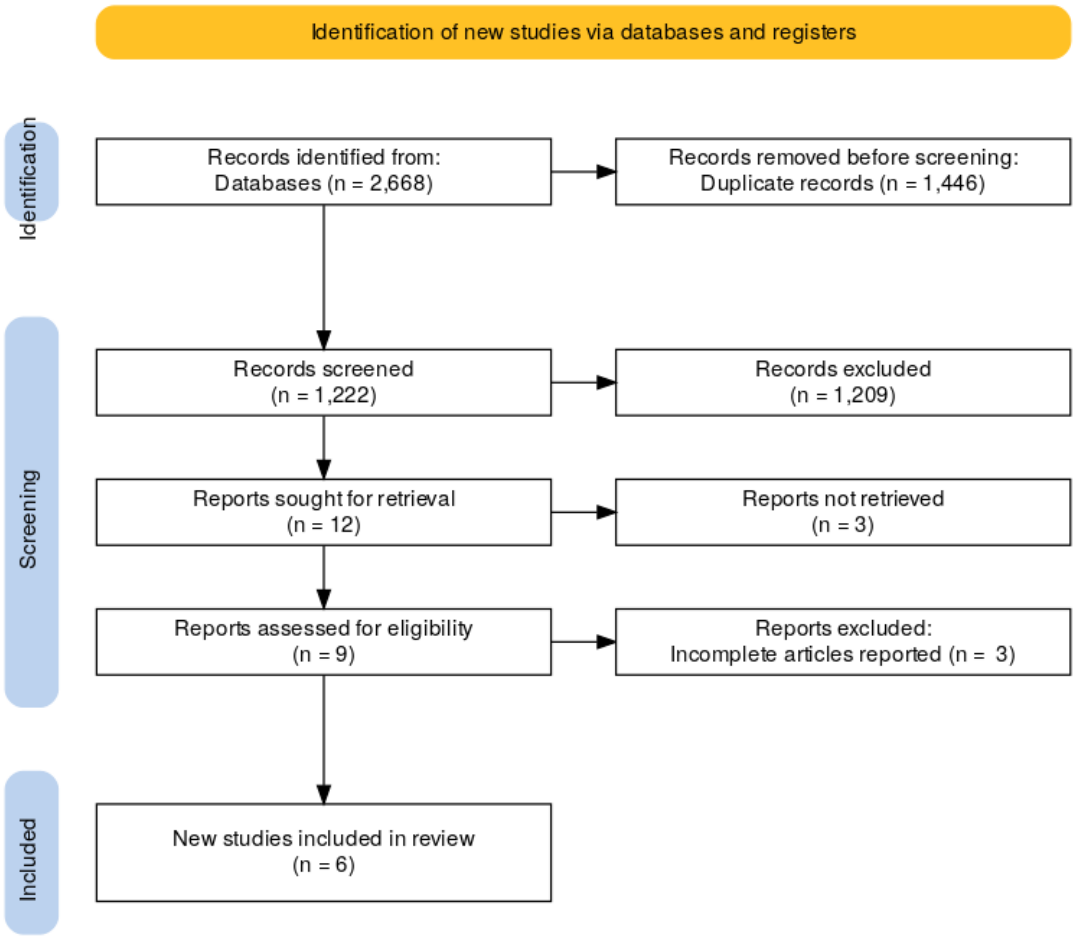

Figure 2. PRISMA flow chart

Table 1. Characteristics of included studies

Author	***Study***	***Region***	***Age/***	***Fungal***	***Medical***	***Symptoms***

(Year)	*Design*		*Gender*	*Organism*	*History*	
Mariana et al. (2019)	CR	US	41/F	*Purpureocillium*	SCL wearer with poor hygiene	OS: Pain and redness
			72/F		SCL wearer	OD: Pain and blurred vision
Christine et al. (2024)	CS	US	87/F	Paecilomyces	Recurrent herpetic anterior uveitis OS; Bilateral POAG	OS: Pain and blurred vision
			77/M		PKP for CU; bilateral glaucoma	OD: Pain
			48/M		SCL wearer	OD: Pain and worsening vision
Elmer et al. (2007)	CS	US	29/M	Fusarium	N/A	OS: Foreign-body sensation
Altun et al. (2014)	CS	Turkey	43/F	Fusarium	SCL wearer	OD: Pain and redness
			62/M		Non-penetrating ocular trauma with organicmaterial (bough)	OD: Redness and stinging
			14/M		SCL wearer, DM Tipe I	OD: Redness, stinging, and a burning sensation
Michael et al. (2014)	CR	US	57/M	*Paecilomyces*	SCL wearer with poor hygiene	OD: Irritation, pain, photophobia, and worsening vision
W E Sponsel et al. (2002)	CR	US	42/F	Fusarium	SCL wearer	OS: Pain

Table abbreviations: CR: Case Report, CS: Case Series, CU: Corneal Ulcer, F: Female,M: Male, N/A: Not available, OD: Oculus dexter (Right eye), OS: Oculussinister (Left eye), POAG: Primary Open-Angle Glaucoma, SCL: Soft Contact Lenses, US: United States

Table 2. Demographic and characteristics data of included studies

Demographics (%)	
Gender	
Male	6 (54,54%)
Female	5 (45,45%)
Region	
United States	9 (81,81%)
Turkey	2 (18,18%)
Age	
< 50	6 (54,54%)
> 50	5 (45,45%)
Fungal Organism	
Fusarium species	6 (54,54%)
Paecilomyces species	4 (36,36%)
Purpureocillium species	1 (8,33%)
Medical History	
SCL	7 (63,63%)
Glaucoma	2 (18,18%)
Trauma	1 (9,09%)
DM Type 1	1 (9,09%)
Symptoms	
Pain	8 (72,72%)
Worsening vision	4 (36,36%)
Redness	3 (27,27%)
Others	2 (18,18%)

Table 3. Detail Interventions And Findings Of Included Studies

Author (Year)	Age/ Gender	Ocular Examinations	Interventions	Findings
Mariana et al. (2019)	41/F	VA (OD; OS): 20/20; HM central corneal ED, infiltrate, stromal oedema, hypopyon and marked ciliary and conjunctival injection.	A patient with a severe eye infection was initially treated with topical ofloxacin and clotrimazole for three weeks without corneal cultures. Once cultures were obtained, she was started on fortified antibiotics and intravenous ciprofloxacin, but no fungal infection was detected. Despite some early improvement, the condition worsened, requiring stronger antibiotic and antifungal treatments. After 40 days, her infection progressed to a central descemetocele, necessitating	After starting oral posaconazole (400 mg twice daily), the patient experienced symptomatic improvement within a week, with VA increasing from hand motion to 20/200. After two months, no inflammation or fungal recurrence was observed, and her BCVA improved to 20/100. Posaconazole was gradually tapered but discontinued four months later due to

			a corneal transplant (tectonic penetrating keratoplasty). Following surgery, her vision temporarily improved, but complications arose, including endothelial infiltrate and hypopyon. A fungal infection caused by *Purpureocillium* was later identified, prompting aggressive antifungal therapy with intracameral voriconazole, amphotericin B, and oral posaconazole. However, the infection persisted, leading to a second corneal transplant three months later.	elevated serum creatinine and hypokalemia. Despite stopping the medication, the infection did not return, and kidney function normalized after eight months.
Christine et al. (2024)	72/F	VA (OD; OS): 20/600; 20/30 5 mm central perforated CU with clear peripheral cornea	A patient with a fungal eye infection was initially treated with multiple topical antibiotics, intraocular voriconazole and amphotericin B, and oral voriconazole and doxycycline. Since the infection persisted, oral posaconazole (300 mg daily) was introduced for two weeks.	After receiving posaconazole, the patient's keratomycosis seemed to have fully resolved. This case highlights *Paecilomyces* as a rare but persistent cause of infectious keratitis, often requiring multiple treatments. It underscores the importance of aggressive therapy and suggests posaconazole as a crucial treatment option for resistant infections.
	87/F	VA (OD; OS): 20/30; 20/500 inferotemporal corneal infiltrate with neovascularization	The patient initial therapy was loteprednol, travoprost, and natamycin, along with intraocular voriconazole and amphotericin B. Oral voriconazole, doxycycline, and valaciclovir were also administered. When the infection did not improve, the treatment was changed to oral posaconazole.	
	77/M	VA (OD; OS): HM; CF at 3 ft infiltrate was noted in the bed of the epithelial defect on the donor cornea	The patient was initially treated with a combination of topical medications, including antibiotics, antifungals, and corticosteroids, along with oral voriconazole and doxycycline. Due to a lack of improvement, the treatment was changed to oral posaconazole.	
Elmer et al. (2007)	48/M	VA (OD; OS): HM; N/A	Patient initially treated with topical trifluridine after	Oral posaconazole was administered to

	OD: 2.5-mm round paracentral stromal infiltrate with indistinct margins temporal to the visual axis	being misdiagnosed as having herpes simplex keratitis. Corneal cultures later identified Fusarium, leading to a switch to topical natamycin and systemic fluconazole. Despite additional antifungal treatments, severe pain and inflammation necessitated a corneal transplant (penetrating keratoplasty). Post-surgery, fungal hyphae were found penetrating the Descemet membrane, and endothelial haze developed. Even with intensified antifungal therapy (voriconazole and amphotericin B), *Fusarium solani* persisted, requiring a corneal-scleral graft. After failing multiple treatments, oral posaconazole was introduced alongside topical amphotericin B.	all patients, which promptly decreased intraocular pain and inflammation and led to the infection's spontaneous resolution. Deep Fusarium keratitis is challenging to treat, and endophthalmitis is often the outcome. Posaconazole, which is well-known for its strong tissue penetration and effectiveness in treating systemic Fusarium infections, was able to successfully cure three cases of pan-resistant keratitis and/or endophthalmitis.
29/M	VA (OD; OS): N/A; HM OS: 3.5 5.0-mm central keratitis	The patient was initially treated with topical gatifloxacin, trifluridine, and atropine, which were ineffective. Cultures identified a Fusarium species resistant to amphotericin B, natamycin, and fluconazole. Patient underwent two corneal transplants due to persistent infection. Voriconazole was introduced but had to be discontinued due to systemic toxicity. After the second transplant, oral posaconazole and a topical antifungal solution were administered.	
43/F	VA: N/A OD: Progression of the keratitis and development of crystalline branching infiltrates	Initially treated with topical vancomycin, gatifloxacin, and systemic acyclovir. *Fusarium* was identified, prompting a switch to natamycin, amphotericin B, and fluconazole. After six weeks, antifungal therapy changed to voriconazole, but the infection worsened, leading to a corneal transplant. Persistent fungal presence required discontinuation of voriconazole (due to	

			hepatotoxicity) and a patch graft with amphotericin injection. As *Fusarium* continued to grow, oral posaconazole was introduced while maintaining topical antifungals.	
Altun et al. (2014)	62/M	VA: N/A OD: 5.0 × 4.5 mm deep corneal ulcer, stromal infiltration with a clear corneal periphery, and no hypopyon in the right eye	Patient was treated with various eye drops, including fluorometholone and tobramycin, for a week without improvement. Despite multiple antibiotic and antifungal treatments (natamycin, voriconazole, fluconazole, and amphotericin B), the infection worsened, causing corneal thinning and increased pain. On the 12th day, oral and topical posaconazole were introduced.	The patient showed significant improvement within days—clinical appearance improved in four to five days, and after two weeks, the ulcerations had healed, conjunctival hyperemia resolved, and corneal vascularization regressed.
	14/M	VA: N/A OD: 4.0 × 3.0 mm area of paracentral corneal ulcer, deep corneal stromal infiltration, 2 mm hypopyon		
Michael et al. (2014)	57/M	VA (OD; OS): 20/100; 20/15 OD: large corneal epithelial defect with a peripheral infiltrate.	Initial treatment included oral voriconazole, multiple topical antifungals (amphotericin, natamycin, voriconazole, and miconazole), and intracameral/subconjunctival injections of voriconazole and miconazole. However, the infection did not improve, leading to the addition of oral posaconazole twice daily.	After one week of posaconazole treatment, the patient's symptoms and visual acuity improved significantly, from counting fingers to 20/200. By six weeks, inflammation and fungal infection were no longer present. After five months, the cornea remained clear, and the patient achieved a best-corrected visual acuity (BCVA) of 20/20 after discontinuing antifungal therapy.
W E Sponsel et al. (2002)	42/F	VA(OD; OS): 20/20 OS: Deep central corneal ulcer, 2-3 mm pericentral corneal ulcer.	The patient was initially treated with tobramycin and high-dose fluoroquinolones. When the infection persisted, keratomycosis was diagnosed, and treatment was escalated to high-dose amphotericin B (topical and intravenous), natamycin,	After just one week of posaconazole treatment, the patient's condition significantly improved, with an infectious fibrin clot disintegrating and the corneal periphery

		ketoconazole, and other topical antibiotics. However, the infection spread to the corneal periphery, and cultures confirmed *Fusarium* resistant to amphotericin B. The treatment was then switched to oral posaconazole and hourly topical posaconazole.	clearing. On September 20, 2000, the infection was discovered after additional treatment, necessitating an urgent penetrating keratoplasty to cure a corneal ulcer. The fibrin clot largely disappeared within a week, and the patient's vision improved. By October 30, 2000, corticosteroids were on the market, and in January 2001, elective cataract surgery was carried out. The patient's vision remained stable sixteen months later, with good peripheral vision and a very favorable outlook for further eye rehabilitation.

Table abbreviations: BCVA: Best-Corrected Visual Acuity, CF: Counting fingers, CU: Corneal Ulcer, EP: Epithelial Defect, F: Female, HM: Hand Motion,M: Male, N/A: Not available, OD: Oculus dexter (Right eye), OS: Oculussinister (Left eye), PKP: penetrating keratoplasty, SCL: Soft Contact Lenses, US: United States, VA: Visual Acuity

DISCUSSION

Studies discussing posaconazole's effectiveness in treating refractory keratomycosis are quite rare. To the best of our knowledge, we have presented the results of the included research that examined and contrasted posaconazole with other antifungal medications that are associated with this subject. The results of two investigations show that oral posaconazole was effective in treating refractory *P. lilacinus* (*Paecilomyces lilacinus*) keratitis cases that were resistant to both traditional antifungals and other second-generation triazoles. Posaconazole may be an effective option for treating resistant *Paecilomyces* keratitis. This conclusion is supported by additional research that describes *P. varioti* (*Paecilomyces varioti)* and *P. lilacincus* are the two species of *Paecilomyces* that infect humans and cause illness. *P. varioti* is resistant to voriconazole, susceptible to amphotericin B, and thermophilic (growing at 50–60°C). *P. lilacinus* is susceptible to voriconazole and posaconazole but resistant to amphotericin B[26].

Most of the patients were men over the age of fifty. Among men, keratomycosis was more common[27]. Men had a higher risk of developing keratomycosis than women, according to a recent Chinese study[28]. This is probably because agricultural workers—who are typically men—are more

likely to sustain traumatic corneal injuries[29]. However, recent research has indicated that the higher prevalence of traumatic corneal injuries in male agricultural laborers may not be the only factor contributing to the higher incidence of keratomycosis in men. The gender gap observed in keratomycosis cases may potentially be influenced by genetics and hormonal variations[30]. Elderly patients are more likely than younger patients to have corneal perforations[31]. The cornea becomes less sensitive as a result of various circumstances, including as aging, which is brought on by abnormalities in the eye's surface. This hinders wound healing and increases the cornea's susceptibility to infection[32].

One study reported elderly women with no endoplaque was seen, and the fungal invasion disappeared two weeks after posaconazole was started. However, following a 4-week treatment of posaconazole, the patient experienced hypertensive urgency, which was probably brought on by the medication. Clinical clearance of the stromal infiltration and endoplaque was observed one month later. Posaconazole most certainly caused adrenal hyperplasia, which PET imaging would not detect, and elevated catecholamine and metanephrine levels exacerbated hypertension[33]. Paecilomyces is an uncommon cause of infectious keratitis, and three identical cases in elderly people involved prolonged, resistant infections that required multiple treatments. These cases, supported by advanced imaging, highlight the importance of early and intensive treatment, with posaconazole being crucial. After a three-week course of posaconazole, the ocular surface healed well, and no recurrence of microbial keratitis was observed 14 weeks after surgery. We discovered that *S. aureus* (*Staphylococcus aureus)* was identified as the most common bacterium linked to recurrent infections, consistent with prior findings[34].

According to Elmer et al. All patients were given oral posaconazole, which quickly reduced intraocular pain and inflammation and caused the infection to go away on its own[35]. Treatment for deep Fusarium keratitis is hard to treat, and endophthalmitis is frequently the result. Posaconazole, however, is well known for its strong tissue penetration and effectiveness in treating systemic *Fusarium* infections, and it was used to treat three cases of pan-resistant keratitis and or endophthalmitis. Six cases of *Fusarium* keratitis successfully treated with oral posaconazole were discovered in the evaluated publications. Posaconazole was used topically in a *F. solani (Fusarium solani)* case that progressed to endophthalmitis. An Iranian study found excellent susceptibility of *F. solani, F. oxysporum, F. fujikuroi, F. falciforme, and F. proliferatum* to posaconazole, but *F. keratoplasticum* showed resistance. However, studies from Spain and the Netherlands reported significant posaconazole resistance across all *Fusarium* species. Further research is needed to evaluate posaconazole's effectiveness in *Fusarium* keratitis treatment[36].

According to published research, patients of keratomycosis progressed to endophthalmitis at a higher rate than those of bacterial keratitis[37].

Posaconazole, like all triazoles, inhibits the cytochrome P450 family member fungal lanosterol 14 alpha-demethylase enzyme (CYP51)[38]. By doing this, posaconazole prevents the production of ergosterol, the main sterol in fungal cell membranes and a crucial factor in determining the integrity of cell membranes, the function of membrane-associated proteins, and cell cycle progression[39]. There is currently no parenteral formulation of posaconazole; it is taken orally as a suspension at a dose of 800 mg daily. Up to the suggested daily dosage, serum medication concentrations rise dose-proportionately; after that, they stop rising[40]. Posaconazole is a broad-spectrum oral triazole that works against a variety of molds and yeasts. Although it has been recorded, posaconazole resistance has not proven common thus far[41]. For the prevention and treatment of a variety of fungal processes, posaconazole seems to be a useful and promising addition to the antifungal arsenal. Posaconazole should likely be saved for prophylaxis in patients who are at high risk of developing an invasive fungal infection, as a salvage treatment for infections that are resistant or refractory, or for patients who are intolerant to other treatments[42].

The case presented by W. E. Sponsel et al. After just one week of posaconazole treatment, the patient's condition significantly improved, with an infectious fibrin clot disintegrating and the corneal periphery clearing. The patient's vision remained stable with good peripheral vision and the outlook for further eye rehabilitation was extremely favorable[43].

CONCLUSION

In conclusion, posaconazole possibly effective for the cases of refractory keratomycosis, especially for refractory cases, posaconazole is essential to a successful course of treatment. The findings can be a basis for further studies with high-level evidence studies such as cohort or clinical trials to confirm the efficacy of posaconazole for refractory keratomycosis.

CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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