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Review

Eumycetoma Medical Treatment: Past, Current Practice, Latest Advances and Perspectives

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Abstract: Mycetoma is a neglected tropical disease that is associated with poor communities and socioeconomically impaired individuals in the tropical and sub-tropical areas. Interestingly, the disease is caused by either bacteria (actinomycetoma) or fungus (eumycetoma). The latter form of the disease, eumycetoma, is the most common type in Africa. Eumycetoma is characterized by a prolonged disease duration and low cure rate. The effective case management of eumycetoma largely depends on the accurate diagnosis and identification of the causative agent to the species level and evaluating its susceptibility to the available drugs. This review summarizes the currently available and used antifungal agents for the treatment of eumycetoma and discusses optimizing the newly developed antifungals as a potential second line for eumycetoma treatment.

Keywords: eumycetoma; antifungal; in vitro susceptibility; animal models

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1. Introduction

Mycetoma is a neglected chronic granulomatous tropical disease that can be caused either by bacteria (actinomycetoma) or fungi (eumycetoma) [1–5]. Mycetoma infection involves the skin and subcutaneous tissues with general clinical presentation characterized by painless swelling, multiple discharging and draining sinuses, and the presence of grains. Both infections are indistinguishable clinically which increase the diagnostic challenge imposed by the involvement of several species of bacteria and fungi in the development of the disease [6,7]. The prevalence of the causative agents varies from one geographical region to another depending mostly on the climate, humidity, and personal hygiene. Most of the reported cases of mycetoma were from Sudan, Mexico, and India [8]. In Africa, the most common form of the disease is eumycetoma, and several cases of this infection have emerged recently in eumycetoma-free areas [8]. In Sudan, the most predominant causative agent was found to be the *Madurella mycetomatis* [1]. The treatment of eumycetoma is based on the administration of antifungals combined with surgical excision after encapsulation; thus, the treatment of the patients might take a long time [9]. The aim of this review is to present the current antifungal agents which are commonly used for the treatment of eumycetoma as well as discussing the currently available and potentially new antifungals that can be optimized for the treatment of eumycetoma.

2. Materials and Methods

An extensive search was undertaken in the literature review in the PubMed, Embase, and Scopus databases for all published papers reporting eumycetoma treatment using the MESH searching terms "eumycetoma treatment". We also tracked other reports in the lists of references. Furthermore, we reviewed the proceedings from relevant symposia and oral presentations.

3. Eumycetoma Causative Agents

Numerous fungi are considered as causative agents for eumycetoma and they differ from each other in their response to antifungal therapy. In addition, they can be clinically classified according to the color of the grains produced by the fungus into three groups, namely: pale grains eumycetoma, white grains, yellow grains, and black grains. Classifications according to the causative agent of eumycetoma include *Aspergillus flavus*, *Asp. nidulans*, *Cladophialophora bantiana*, *Curvularia* (*Cur.*) *spinifera*, *Corynespora cassicola*, *Cur. geniculata*, *Cur. lunata*, *Cylindrocarpon cyanescens*, *Cyl. destructans*, *Exophiala jeanselmei*, *Exserohilum rostratum*, *Fusarium falciforme* (formerly *Acremonium* (*A*) *falciforme*), *Fusarium moniliforme*, *F. oxysporum*, *F. solani*, *Leptosphaeria senegalensis*, *L. tompkinsii*, *Madurella mycetomatis*, *M. grisea*, *M. fahalii*, *Neotestudina rosatii*, *Phaeoacremonium krajdenii*, *Plenodomus avramii*, *Polycytella hominis*, *Sarocladium kiliense* (formerly *A. kiliense*), *Scedosporium* (*Sc.*) *boydii*, and *Sc. apiospermium* [10–12]. The most common species that are responsible for more than 90% of the globally reported cases include *M. mycetomatis*, *M. grisea*, *Sc. boydii*, and *L. senegalensis* [10–12].

4. Currently Used Drug for Eumycetoma

Based on our experience, the use of antifungals alone for the treatment of eumycetoma is not sufficient for the absolute cure of the patients. Therefore, it is commonly combined with the surgical intervention; this contributes to decrease the fungal load and thus shift the immune response to Th1. This is considered significant enough to cause a curative response leading to the elimination of eumycetoma [13–15]. The major importance of administrating antifungals to our patients is that it will reduce the size of the lesion making it well encapsulated. This will eventually enable the surgeon to have better clean excisions of the lesions and limit the permanent skin disfiguring affect [16]. Several antifungal drugs have been used over the last decades for the treatment of eumycetoma. The first drug ketoconazole was used for several years since 1980s as the first drug of choice for eumycetoma in a dosage of 400 mg/day; its use has been ceased after a recommendation from the Food Drug Administration (FDA) as they proved that this drug leads to severe liver injury and adrenal insufficiency [17]. Ketoconazole was later substituted by itraconazole 200 mg/day BD. However, a 400 mg/day itraconazole was recommended as the first line drug for eumycetoma with lesions of moderate and large size (5–10 cm and more than 10 cm, respectively) and/or bone involvement for six months, and then it would be supported by surgical excision. On the other hand, for the small lesion size a wide local excision is recommended followed by administration of 400 mg/day itraconazole for 3 months, and then the lesion is assessed by ultrasound imaging. However, the cure rate for combining the itraconazole with surgical removal of lesion is still very low with at least 33% a recurrence rate among the patients.

Therefore, several azoles were investigated in clinical trials including voriconazole as a treatment option for *M. mycetomatis* and *Sc. apiospermum* [18–32], and posaconazole which has been proven to be effective in two cases of *M. mycetomatis*, three cases due to *M. grisea*, and a single case due to *Sc. apiospermum* [20]. Interestingly, fosravuconazole is currently undergoing human trials (NCT03086226). Liposomal amphotericin B was also used for the treatment of eumycetoma; however, this drug was shown to be associated with a high rate of adverse events and relapse rates [21]. Another treatment option was the administration of terbinafine in a high oral dose of 500 mg twice/day and shown to treat a case of eumycetoma caused by *Exophiala jeanselmei* [22,23]. Furthermore, N'Diaye et al. assessed the efficacy and safety of terbinafine in the treatment of eumycetoma caused by *M. mycetomatis*, *L. senegalensis*, and two unknown fungal species. Their results showed that

terbinafine is an efficient drug for the treatment of eumycetoma with a minimum treatment duration of 24 weeks [24].

5. In Vitro Activity

In vitro studies of different alternatives drugs have demonstrated potent antifungal activities against numerous fungal species that are involved in the development of eumycetoma. Van de Sande et al. have conducted several studies demonstrating the susceptibility pattern of different antifungal drugs including ketoconazole, itraconazole, fluconazole, voriconazole, amphotericin B, and flucytosine against 36 isolates of *M. mycetomatis* [33–35]. Researchers have used different techniques including CLSI broth dilution assay, Sensititre YeastOne test, and the XTT test to assess and evaluate the efficacy of different drugs against different fungal species that cause eumycetoma. Their results showed that ketoconazole, itraconazole, and voriconazole were the most active and potent antifungals (Table 1). The minimum inhibitory concentration (MIC) for ketoconazole ranged from less than 0.016–1 μg/mL, and 0.125 μg/mL was needed to inhibit 90% of the isolates, while for itranconazole MIC showed a range of <0.016 to 0.5 μg/mL and only 0.064 μg/mL was needed to inhibit 90% of the strains. Furthermore, the MIC for voriconazole ranged from <0.016 to 1 μg/mL and a concentration of 0.125 μg/mL was needed for the inhibition of 90% of the isolates. On the contrary, the isolates were found to be less susceptible to the non-azole antifungal including amphotericin B, which demonstrated a MIC in range between <0.016 and 4 μg/mL, and a concentration of 2 μg/mL was required to inhibit 90% of the strains. As for the flucytosine, all the isolates were found to be resistant for this antifungal agent [33]. Moreover, in vitro susceptibility patterns for ketoconazole, itraconazole, posaconazole, fluconazole, and voriconazole were assessed against different *Madurella* species including *M. mycetomatis*, *M. tropicana*, *M. pseudomycetomatis*, and *M. fahalii*, all of which were found to be susceptible except for *M. fahalii*, which was found to be resistant to itranconazole (Table 1) [34].

Table 1. In vitro susceptibility, clinical efficacy, and dose of current antifungal agents against Eumycetoma.

Antifungal	Invitro	Human Infection	Route	Dose
		Azole Antifungal		
Ketoconazole	Active	Variable efficacy	Oral	400–800 mg
Itraconazole	Active	Variable efficacy	Oral	200–400 mg
Voriconazole	Active	Effective in few cases	Oral	200 mg
Posaconazole	Active	Effective in few cases	Oral	400 mg
Isavuconazole	Active	No data	NA	NA
Fosravuconazole	Active	Clinical Trial (NCT03086226)	Oral	300–400 mg
Fluconazole	Not effective	Not effective		
		Echinocandins		
Caspofungin	Not active	No data		
Anidulafungin	Not active	No data		
Micafungin	Not active	No data		
		Orotomides		
Olorofim	Active	Clinical Trial (NCT03583164)	Oral	30–300 mg

However, due the high cost of most antifungal drugs and the fact that mycetoma patients are mostly of low socioeconomic status, a new drug was developed to be affordable to the poor patients [33]. This was triazole ravuconazole, which revealed an excellent activity against 23 isolates of M. mycetomatis, showing MIC values significantly lower (0.002 and 0.031 μg/mL) than those presented by the azoles tested (itraconazole and ketoconazole) [35].

Nevertheless, the azole antifungals were also investigated against *Chaetomium atrobrunneum* which is considered as a newly discovered a causative agent producing black grains. The in vitro testing was conducted using a YeastOne Sensititre kit (Thermo Fisher Scientific, Germany) and the assay run against itraconazole, posaconazole, and fluconazole.

The fungus was found to be susceptible to itraconazole and posaconazole with MIC of <0.06, and resistance to the fluconazole with MIC = 256 μg/mL [36].

Another class of antifungals that have been tested against *M. mycetomatis* included echinocandins. This class of antifungal agents inhibits the synthesis of 1, 3-β-glucan, the main component of the fungal cell wall. The in vitro susceptibility test, including caspofungin, anidulafungin, and micafungin, was assessed against 17 clinical isolates of *M. mycetomatis*. The results showed that all isolates were resistant to echinocandins [37]. However, the exact mechanism of such resistance has not yet been elaborated and needs further research to be fully understood.

The allylamine terminafine has also been tested against *M. mycetomatis* and *M. pseudomycetomatis*, and both species were found to be moderately susceptible to that antifungal drug [38,39]. Interestingly, a new class of antifungal drugs such as orotomides was recently used for the treatment of the fungal infections. Olorofim or F901318 inhibits the fungal enzyme dihydroorotate dehydrogenase (DHODH) leading to obstruction of the pyrimidine biosynthesis pathway [40,41]. Many studies were carried out to demonstrate the in vitro activity of olorofim against several fungal species [42–49]. These studies have illustrated that this drug is active against azole-resistant *Aspergillus* species [42–45], *Scedosporium* species [46], and *Fusarium proliferatum* [47]. Olorofim was assessed against 21 isolates of *M. mycetomatis* and compared to that of itraconazole [48]. The study showed that MIC values for the former drug ranged between 0.004–0.125 μg/mL, whereas for Itraconazole they ranged between 0.008–0.25 μg/mL, suggesting that *M. mycetomatis* was more susceptible to olorofim than itraconazole [48]. Similar results were obtained when the drug was assessed against different *Scedosporium* and *L. prolificans* species, in comparison toto other antifungals such as itraconazole, voriconazole, and posaconazole [49]. Furthermore, olorofim has showed activity against some uncommon eumycetoma causative agents such as *Microascus* and *Scopulariopsis* species [50]. These species have displayed a reduced susceptibility to the azoles antifungal; additionally, the drug was promising for the treatment of *Acremonium* species, *Paecilomyces variotii*, with a high MIC for voriconazole [51–53].

6. In Vivo Activity

Scarce animal models were designed for studying *M. mycetomatis* including murine, rabbit, and invertebrate (the larvae of *Galleria mellonella*) models [54,55], and only a single model has evaluated the therapeutic effect of antifungals for *M. mycetomatis* infection [55]. The model of the *Galleria mellonella* larvae was used to evaluate the efficacy of amphotericin B, itraconazole, and terbinafine individually as monotherapy as well as when combined with each other for treating *M. mycetomatis* infection. The result showed that the treatment of the infected larvae with amphotericin B enhanced the survival of the model [56]. Several experimental models were developed for *Sc. apiospermium* including mouse and guinea pig; these models were used to test the efficacy of voriconazole and posaconazole in the treatment of such infection [57–60]. In vivo experiments showed that posaconazole was effective only at high doses (≥25 mg/kg) in a murine model with a disseminated *Sc. apiospermum* infection, while itraconazole was not effective and demonstrated only a minimal effect [59].

7. Adverse Effects

Since the azoles are considered as the first line treatment, it is therefore critical to detect and observe the drug interaction of these azoles. For optimal drug absorption it is very important that they are not administered with any antacids because this will reduce their absorbance. Furthermore, if the patient used a calcium channel inhibitor with these azoles, edema is likely to occur and is prominent in such scenarios. Moreover, co-administration with rifampin, phenytoin, and histamine 2 receptor antagonist leads to a reduction of the azole levels in the plasma [61].

Ketoconazole induces liver toxicity, gynecomastia, dry lips, hyperpigmentation, and decreased libido [62]. Additionally, itraconazole is contraindicated in patients with ventricular dysfunction. Posaconazole was found to cause fever, vomiting, nausea, diarrhea,

abdominal pain, and skin rash as well as prolonged QT interval [63]. On the other hand, voriconazole, which is considered as the most effective drug for the treatment of various invasive fungal infections including mycetoma, was found to cause prolonged QT interval which may precede life threatening arrhythmias (NCT04502355).

For all azoles it is mandatory to monitor the liver function test and if the patient presented with elevated liver function test readings, the treatment should be discontinued, especially if the parameter was markedly elevated. On the contrary, if it is mildly elevated the dose will be reduced to half of the full dose [64].

For terbinafine the most common side effects were headache, diarrhea, rash, itching, neutropenia, leukopenia, and abnormal liver function tests, thus close monitoring for patients is required [65].

8. New Target for New Hope

8.1. Non-Steroidal Anti-Inflammatory Drugs (NSAID)

NSAID was used for several decades as a treatment modality for rheumatological disorders and it is used widely as an analgesic drug [66]. Despite their current use these drugs contain many agents that demonstrate some antimicrobial activities [67]. Recent studies reflected the power of these drugs to inhibit the growth of the microorganisms. For instance, a study conducted by Alem and Douglas in 2004 reported the ability of aspirin to inhibit the growth of *Candida albicans* in the biofilm [66]. Furthermore, Zhou et al. have demonstrated the enhanced effectiveness of combination therapy once aspirin was co-administered with amphotericin B against *Candida* spp. [68]. Interestingly, Dupont et al. have succeeded in curing a patient with eumycetoma caused by *M. mycetomatis* with a history of bone involvement; the treatment strategies implied that the treatment of patients with NSAID, diclofenac (100 mg per day) combined with the antifungal treatment, showed a pronounced improvement within the first week of initiating the treatment. Then after two months, clinical examination was normal, with no pain, inflammation, nodules, or fistulae [69,70].

8.2. Olorofim

Olorofim is currently considered as the most potent promising agent and it is currently enrolled in clinical trials for the treatment of various fungal infections including deep mold infections as well as invasive fungal infections caused by *L. prolificans*, *Scedosporium* spp., *Aspergillus* spp., and other fungi that have been resistant to the currently used antifungal agents. The major advantage of this promising drug is that it has a different mode of action: its mechanism of action targets the pyrimidine biosynthesis, and thus can be used for the treatment of fungi infections that are resistant to azoles and amphotericin B. Currently the drug is undergoing a single arm phase IIb clinical trial (NCT03583164) and is used for the treatment of invasive fungal infection including refractory aspergillosis, infections caused by *Scedosporium* species. Additionally, it has been investigated as alternative treatment for patients intolerant to the available antifungal drugs. In 2019, the FDA has declared olorofim as an orphan drug for the treatment of invasive aspergillosis, infection by *Lomentospora* and *Scedosporium* species, as well as invasive fusariosis [71].

9. Conclusions

There are several drugs available for the treatment of different mycetoma infections; however, most of them have serious side effects or adverse outcomes on patients' overall health. Additionally, some of the causative agents have developed resistance to the currently used drugs. Therefore, these treatments need to be administered with care and under direct supervision of the treating physician with a close monitoring of the patient's progress and the impact of drug use on the patient's body, particularly the liver functions. It is very important to highlight that the prevalence of adverse side effects of the available drugs indicates the global neglect and limited investment in developing a more safe and proper treatment for mycetoma infections, which could be attributed to the fact that mycetoma is mainly prevalent among poor individuals, and, therefore, does not promise financial returns for drug developers. More importantly, the increasingly developing resistance

to the currently available drugs urges the global health community and its partners, including private companies working in drug development and major donors, to invest and collaborate in the development of safe, effective, and affordable alternatives to the poor communities' drugs.

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