Eumycetoma Medical Treatment

Subjects: Tropical Medicine

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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.

eumycetoma antifungal

1. Introduction

Mycetoma is a neglected chronic granulomatous tropical disease that can be caused either by bacteria (actinomycetoma) or fungi (eumycetoma) [1][2][3][4][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].

2. Currently Used Drug for Eumycetoma

Based on previous 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 [10][11][12]. The major importance of administrating antifungals to the 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 [13]. 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 [14]. 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* [15][16][17][18][19][20][21][22][23][24][25][26][27][28][29], 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* [17]. 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 [18]. 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* [19][20]. 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 [21].

3. New Target for New Hope

3.1. 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 [30]. Despite their current use these drugs contain many agents that demonstrate some antimicrobial activities [31]. 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 [30]. Furthermore, Zhou et al. have demonstrated the enhanced effectiveness of combination therapy once aspirin was co-administered with amphotericin B against *Candida* spp. [32]. 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 [33][34].

3.2. 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 [35].

4. 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.

References

1. Siddig, E.E.; Mhmoud, N.A.; Bakhiet, S.M.; Abdallah, O.B.; Mekki, S.O.; El Dawi, N.I.; Van de Sande, W.; Fahal, A.H. The Accuracy of Histopathological and Cytopathological Techniques in the Identification of the Mycetoma Causative Agents. PLoS Negl. Trop. Dis. 2019, 13, e0007056.
2. Oladele, R.O.; Ly, F.; Sow, D.; Akinkugbe, A.O.; Ocansey, B.K.; Fahal, A.H.; van de Sande, W.W.J. Mycetoma in West Africa. Trans. R. Soc. Trop. Med. Hyg. 2021, 115, 328–336.
3. Fahal, A.H. The Khartoum call for action Khartoum, Sudan—2019. Trans. R. Soc. Trop. Med. Hyg. 2021, 115, 295–296.

4. Kébé, M.; Ba, O.; Mohamed Abderahmane, M.A.; Mohamed Baba, N.D.; Ball, M.; Fahal, A. A study of 87 mycetoma patients seen at three health facilities in Nouakchott, Mauritania. Trans. R. Soc. Trop. Med. Hyg. 2021, 115, 315–319.
5. Fahal, A.H. Mycetoma: The journey from neglect to recognition as a neglected tropical disease. Trans. R. Soc. Trop. Med. Hyg. 2021, 115, 292–294.
6. Fahal, A.H.; Suliman, S.H.; Hay, R. Mycetoma: The Spectrum of Clinical Presentation. Trop. Med. Infect. Dis. 2018, 3, 97.
7. Verma, P.; Jha, A. Mycetoma: Reviewing a neglected disease. Clin. Exp. Dermatol. 2019, 44, 123–129.
8. Traxler, R.M.; Beer, K.D.; Blaney, D.D.; van de Sande, W.W.J.; Fahal, A.H.; Asiedu, K.B.; Bower, W.A.; Chiller, T. Development of the Global Mycetoma Working Group. Trans. R. Soc. Trop. Med. Hyg. 2021, 115, 437–440.
9. Mahgoub, E. Mycetoma in Sudan: Experience of the Mycetoma Project from 1968 to 1991. Trans. R. Soc. Trop. Med. Hyg. 2021, 115, 287–291.
10. Nasr, A.; Abushouk, A.; Hamza, A.; Siddig, E.; Fahal, A.H. Th-1, Th-2 Cytokines Profile among Madurella mycetomatis Eumycetoma Patients. PLoS Negl. Trop. Dis. 2016, 10, e0004862.
11. Abushouk, A.; Nasr, A.; Masuadi, E.; Allam, G.; Siddig, E.E.; Fahal, A.H. The Role of Interleukin-1 cytokine family (IL-1β, IL-37) and interleukin-12 cytokine family (IL-12, IL-35) in eumycetoma infection pathogenesis. PLoS Negl. Trop. Dis. 2019, 13, e0007098.
12. Siddig, E.E.; Mohammed Edris, A.M.; Bakhiet, S.M.; van de Sande, W.W.J.; Fahal, A.H. Interleukin-17 and matrix metalloprotease-9 expression in the mycetoma granuloma. PLoS Negl. Trop. Dis. 2019, 13, e0007351.
13. Puerta-Arias, J.D.; Pino-Tamayo, P.A.; Arango, J.C.; Salazar-Peláez, L.M.; González, A. Itraconazole in combination with neutrophil depletion reduces the expression of genes related to pulmonary fibrosis in an experimental model of paracoccidioidomycosis. Med. Mycol. 2018, 56, 579–590.
14. US Food and Drug Administration. FDA Drug Safety Communication: FDA Warns that Prescribing of Nizoral (Ketoconazole) Oral Tablets for Unapproved Uses Including Skin and Nail Infractions Continues Linked to Patient Death; US Food and Drug Administration: Madison, WI, USA, 2013.
15. Lacroix, C.; Kerviler, E.; Morel, P.; Derouin, F.; Feuilhade de Chavin, M. Madurella Mycetomatis mycetoma treated successfully with oral voriconazole. Br. J. Dermatol. 2005, 152, 1067–1068.
16. Oliveira, F.M.; Unis, G.; Hochhegger, B.; Severo, L.C. Scedosporium apiospermum eumycetoma successfully treated with oral voriconazole: A case report of a case and review of the Brazilian reports on scedosporiosis. Rev. Inst. Med. Trop. São Paulo 2013, 55, 121–123.

17. Crabol, Y.; Poiree, S.; Bougnoux, M.E.; Maunoury, C.; Barete, S.; Zeller, V.; Arvieux, C.; Pineau, S.; Amazzough, K.; Lecuit, M.; et al. Last generation triazoles for imported eumycetoma in eleven consecutive adults. PLoS Negl. Trop. Dis. 2014, 8, e3232.
18. Hay, R.J.; Mahgoub, E.S.; Leon, G.; al-Sogair, S.; Welsh, O. Mycetoma. J. Med. Vet. Mycol. 1992, 30, 41–49.
19. Agger, W.A.; Andes, D.; Burgess, J.W. Exophiala jeanselmei infection in a heart transplant recipient successfully treated with oral terbinafine. Clin. Infec. Dis. 2004, 38, e112–e115.
20. Rallis, E.; Frangoulis, E. Successful treatment of subcutaneous phaeohyphomycosis owing to Exophiala jeanselmei with oral terbinafine. Int. J. Dermatol. 2006, 45, 1369–1370.
21. N'Diaye, B.; Dieng, M.T.; Perez, A.; Stockmeyer, M.; Bakshi, R. Clinical efficacy and safety of oral terbinafine in fungal mycetoma. Int. J. Dermatol. 2006, 45, 154–157.
22. Lackner, M.; De Man, F.H.; Eygendaal, D.; Wintermans, R.G.; Kluytmans, J.A.; Klaassen, C.H.; Meis, J.F. Severe prosthetic joint infection in an immunocompetent male patient due to a therapy refractory Pseudallescheria apiosperma. Mycoses 2011, 54, 22–27.
23. Morio, F.; Horeau-Langlard, D.; Gay-Andrieu, F.; Talarmin, J.P.; Haloun, A.; Treilhaud, M.; Despins, P.; Jossic, F.; Nourry, L.; Danner-Boucher, I.; et al. Disseminated Scedosporium/Pseudallescheria infection after double-lung transplantation in patients with cystic fibrosis. J. Clin. Microbiol. 2010, 48, 1978–1982.
24. Panackal, A.A.; Marr, K.A. Scedosporium/Pseudallescheria infections. Semin. Respir. Crit. Care Med. 2004, 25, 171–181.
25. Tóth, E.J.; Nagy, G.R.; Homa, M.; Ábrók, M.; Kiss, I.É.; Nagy, G.; Bata-Csörgő, Z.; Kemény, L.; Urbán, E.; Vágvölgyi, C.; et al. Recurrent Scedosporium apiospermum mycetoma successfully treated by surgical excision and terbinafine treatment, a case report and review of the literature. Ann. Clin. Microbiol. Antimicrob 2017, 16, 31.
26. Nesky, M.A.; McDougal, E.C.; Peacock, J.E., Jr. Pseudallescheria boydii brain abscess successfully treated with voriconazole and surgical drainage: Case report and literature review of central nervous system pseudallescheriasis. Clin. Infect. Dis. 2000, 31, 673–677.
27. Porte, L.; Khatibi, S.; Hajj, L.E.; Cassaing, S.; Berry, A.; Massip, P.; Linas, M.D.; Magnaval, J.F.; Sans, N.; Marchou, B. Scedosporium apiospermum mycetoma with bone involvement successfully treated with voriconazole. Trans. R. Soc. Trop. Med. Hyg. 2006, 100, 891–894.
28. Troke, P.; Aguirrebengoa, K.; Arteaga, C.; Ellis, D.; Heath, C.H.; Lutsar, I.; Rovira, M.; Nguyen, Q.; Slavin, M.; Chen, S.C.A. Treatment of scedosporiosis with voriconazole, clinical experience with 107 patients. Antimicrob. Agents Chemother. 2008, 52, 1743–1750.

29. Mellinghoff, I.K.; Winston, D.J.; Mukwaya, G.; Schiller, G.J. Treatment of Scedosporium apiospermum brain abscesses with posaconazole. Clin. Infect. Dis. 2002, 34, 1648–1650.
30. Alem, M.A.; Douglas, L.J. Effects of Aspirin and other nonsteroidal anti-inflammatory drugs on biofilms and blanktonic cells of Candida albicans. Antimicrob. Agents Chemother. 2004, 48, 41–47.
31. Abdul Hussein, A.; Al-Janabi, S. Investigation of anti-dermatophytic effects of non-steroidal anti-inflammatory drugs on trichophyton mentagrophytes and epidermophyton floccosum. Iran. J. Pharm Res. 2011, 10, 547–552.
32. Zhou, Y.; Wang, G.; Li, Y.; Liu, Y.; Song, Y.; Zheng, W.; Zhang, N.; Hu, X.; Yan, S.; Jia, J. In vitro interactions between aspirin and amphotericin B against planktonic cells and biofilm cells of Candida albicans and C. parapsilosis. Antimicrob. Agents Chemother. 2012, 56, 3250–3260.
33. Dupont, B. A non-steroidal anti-inflammatory drug to treat eumycetoma. Lancet Infect. Dis. 2016, 16, 779.
34. Dupont, B.; Datry, A.; Poirée, S.; Canestri, A.; Boucheneb, S.; Fourniols, E. Role of a NSAID in the apparent cure of a fungal mycetoma. J. Mycol. Med. 2016, 26, 86–93.
35. Wiederhold, N.P. Review of the Novel Investigational Antifungal Olorofim. J. Fungi 2020, 6, 122.