
Reprints or correspondence: Dr Dimitrios P. Kontoyiannis, Dept of Infectious Diseases, Infection Control and Employee Health, Unit 402, The University of Texas M.D. Anderson Cancer Center, 1515 Holcombe Blvd, Houston, TX 77030 (dkkontoy@mdanderson.org).

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Reply to Sharma et al and Saukkonen et al

To the Editor—With great interest we read the article by Sharma et al [1] and the accompanying editorial [2], which address the reintroduction of antituberculosis drugs after drug-induced liver injury (DILI), an area that until now has been informed by scanty data. We would like to bring 2 points to wider attention that are of particular relevance to sub-Saharan Africa, where DILI is common and frequently associated with human immunodeficiency virus (HIV) infection.

In South Africa, patients with tuberculosis are treated according to World Health Organization recommendations, with use of fixed-drug combinations of isoniazid, rifampicin, pyrazinamide, and ethambutol for 2 months, followed by 4 months of isoniazid and rifampicin [3]. The use of fixed-drug combinations has many advantages but poses problems in the management of DILI. Sequential reintroduction is difficult, because individual drugs are often not readily available in district hospitals and nonstandard treatment may be more difficult to explain to staff and patients. In agreement with the results of Sharma et al [1], we frequently find that the same drug combination is tolerated on reintroduction, and we suspect that many of the cases of drug-induced hepatotoxicity were actually due to adaptation rather than hepatocellular injury. In sub-Saharan Africa, the high rates of concurrent antiretroviral therapy and high prevalence of chronic hepatitis B further complicate the interpretation of elevated levels of liver enzymes [4]. Additional research is needed to determine thresholds for discontinuing treatment in various scenarios and to identify safe and practical reintroduction regimens that take into account the problem of fixed-drug combinations. In concert with this, national tuberculosis programs should ensure the availability of individual drugs for use in special circumstances.

Our second important observation is the relatively frequent occurrence in this setting of hyperbilirubinemia and jaundice without evidence of hepatocellular damage or cholestasis. This usually occurs during the first few weeks of treatment and is likely to be at least partially related to the use of rifampicin and its dose-dependent interference with bilirubin uptake [5]. The management of isolated hyperbilirubinemia is not covered by most guidelines, and it is not clear whether discontinuation of therapy is required [6]; on the basis of what we have experienced in our practice, it seems safe to continue tuberculosis treatment. The importance of differentiating hyperbilirubinemia from true DILI needs to be clarified in future guidelines.

The future of management of tuberculosis and HIV infection in high-prevalence areas in Africa is with decentralized, integrated care at a primary health care level. We support the call for further research to inform practical guidelines for the assessment and management of DILI in public health tuberculosis and HIV programs.

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T. Heller,1 C. Wallrauch,2 and R. J. Lessells2

1Hlabisa Hospital, Hlabisa, KwaZulu-Natal, South Africa; and 2Africa Centre for Health and Population Studies, University of KwaZulu-Natal, Somkhethla, KwaZulu-Natal, South Africa

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Use of Intralesional Voriconazole for the Treatment of Cutaneous Scedosporium apiospermum Infection

To the Editor—Scedosporium apiospermum is an emerging opportunistic fungus that may infect immunocompetent individuals and may cause life-threatening and often fatal disease among the increasing immunosuppressed patient population [1, 2]. Although S. apiospermum is a ubiquitous mold present in polluted water, soil, and sewage [2], most cases of scedosporiosis have been described in western Europe, Australia, and North America; the reasons for this localized prevalence remain poorly known [3]. This pathogen is characteristically difficult to treat because of its particular resistance to commonly used antifungal drugs [2], even though systemic administration of voriconazole or itraconazole has demonstrated clinically useful activity [1, 4, 5]. We report on a case of successful management of cutaneous S. apiospermum infection with a regimen of intralesional voriconazole as antifungal monotherapy.

A 65-year-old woman presented to the hospital with a 6-month history of multiple papulonodular, painless lesions on the arm and back that, following biopsy, were found to be fungal granulomas. She had no prior history of immunosuppression or recent travel. Examination revealed 4 to 6 cm multiple skin nodules on the right lower arm with a friable, orange-red superficial crater. The patient was taking trimethoprim-sulfamethoxazole prophylaxis for Pneumocystis jirovecii pneumonia and had no history of exposure to fungi. A variety of antifungal drugs, including terbinafine, griseofulvin, and itraconazole, had failed.

Given the resistance of S. apiospermum to commonly used antifungal agents, we explored the use of voriconazole as a systemic agent. Voriconazole is an effective salvage therapy for S. apiospermum infections [5, 6]. The use of voriconazole in a noncutaneous setting may be insufficient to control fungal burden, and therefore, an alternative delivery system was needed to achieve adequate concentrations in the infected tissue. Intralesional voriconazole is an effective treatment for cutaneous infections due to fungi resistant to systemic therapy [7]. Direct injection of voriconazole into the skin lesions might provide adequate concentrations of antifungal agents in infected tissue. Voriconazole has been demonstrated to be effective in treating fungal infections of the skin, with resolution of cutaneous lesions reported in 3 of 7 patients [8]. Voriconazole was chosen for its high lipophilicity and low protein binding, allowing it to penetrate the stratum corneum and remain effective at the site of infection. The potential for systemic toxicity with intravenous voriconazole was considered minimal for patients with skin infections due to S. apiospermum, who are often immunocompromised [6].

Intravenous voriconazole (100 mg every 12 hours) was initiated with a single dose of voriconazole for intralesional injection of the right arm. No local reactions were noted with subcutaneous injection. The patient was treated for 6 weeks, with a complete response confirmed after 4 weeks of voriconazole treatment. The patient was followed up for 1 year, and no relapse was observed. Voriconazole is the most common drug used for the treatment of cutaneous fungal infections. It is known to be efficacious against a variety of fungi, including S. apiospermum, and has been shown to be safe and effective in this population [9]. Voriconazole is an important treatment option for cutaneous scedosporiosis, especially in immunocompromised patients. In this case, we demonstrated that intralesional voriconazole can be a safe and effective treatment for cutaneous S. apiospermum infection. The use of intralesional voriconazole offers several advantages, including improved efficacy and decreased risk of systemic toxicity compared with systemic therapy.


Reprints or correspondence: Dr. Tom Heller, Hlabisa Hospital, Private Bag X5801, Hlabisa 3937, South Africa (ehellan@mdanderson.org).

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the dorsum of the second and third fingers of the right hand (Figure 1). Her medical history was notable for systemic lupus erythematosus and chronic hepatitis C. She had systemic lupus erythematosus–induced immune thrombocytopenia that had been treated with a regimen of oral prednisone (15 mg daily) and azathioprine (15 mg daily) for 1 year before hospitalization. In addition to skin nodules, physical examination revealed swelling and onychomycotic-like changes on the second finger of the right hand. Culture of a sample of the pus obtained after draining the larger nodule grew filamentous mold, which was later identified as S. apiospermum by means of amplification and sequence analysis of its rRNA gene internal transcriber spacer 2 region. The patient declined treatment with oral voriconazole because of its potential hepatotoxic effects and her chronic liver disease. Instead, surgical debridement and intralesional injection of voriconazole at a concentration of 3 μg/mL (once weekly for a treatment period of 2 weeks) were carried out. A few days after administration of the second dose of voriconazole, the size of the nodules had markedly decreased. Three months later, the lesions had completely healed and the second finger appeared normal. Despite maintenance of immunosuppressive therapy, no recurrence of the scedosporiosis has been observed during the 2 subsequent years.

The clinical spectrum of S. apiospermum infection is broad, including mycetoma, localized sinopulmonary or extrapulmonary infections, and disseminated disease [2]. Cutaneous scedosporiosis, in turn, may present as solitary ulcers, infiltrative plaques and nodules, hemorrhagic bullae, or suppurative nodules and ulcers [2]. Nowadays, surgical debridement or drainage, in addition to systemic use of antymycotic drugs, is the recommended treatment [1].

Systemic administration of voriconazole has been demonstrated to be effective in treating scedosporiosis and is usually well tolerated [4]. However, several adverse events have been described, including reversible visual disturbances, hallucinations, abdominal pain, and hepatitis (the last in 5%–10% of patients) [4, 5]. We believe that intralesional administration of voriconazole may decrease some disadvantages associated with oral or intravenous use of the drug, such as potential substantial toxic effects, longer treatment duration, high cost, and drug interactions. This novel therapeutic approach seems to be a promising, cost-effective, and safe option for managing cutaneous S. apiospermum infection, especially in patients with underlying liver disease.

Figure 1. Cutaneous Scedosporium apiospermum infection with papulonodular lesions on the back of the second and third fingers of the right hand.
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Mariola Moreno Azofra,1
José Luis Peña Somovilla,2
Miguel Carrascosa Porras,3
Laura Hurtado Carrillo,1
and Rafael Daroca Pérez2

1Internal Medicine Department, Hospital of Santiago Apóstol, Miranda de Ebro, Burgos,
2Internal Medicine Department, Hospital of San Pedro, Logroño, and 3Internal Medicine Department,
Hospital of Laredo, Laredo, Cantabria, Spain

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Reprints or correspondence: Dr Miguel Carrascosa Porras, Internal Medicine Dept, Hospital of Laredo, Avda Derechos Humanos s/n, 39770 Laredo, Cantabria, Spain (mcarrascosa@hild.scsalud.es).

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