Successful Voriconazole Treatment of Disseminated *Fusarium* Infection in an Immunocompromised Patient

Sophie Consigny, Nathalie Dhedin, Annick Datry, Sylvain Choquet, Véronique Leblond, and Olivier Chosidow

Departments of 1Internal Medicine, 2Hematology, and 3Parasitology-Mycology, Hospital Pitié-Salpêtrière, Assistance Publique-Hôpitaux de Paris, Paris, France

*Fusarium* infection is known to cause major morbidity and mortality in immunocompromised hosts. We report the successful treatment of disseminated *Fusarium* infection with skin manifestations in a severely neutropenic, immunocompromised host with voriconazole, a new second-generation triazole. Voriconazole might be an alternative therapy for patients with neutropenia who have fusariosis that is refractory or unresponsive to amphotericin B or its liposomal formulation.

*Fusarium* is an emerging opportunistic fungal pathogen that can cause severe disseminated infections in immunocompromised patients with neutropenia [1–3]. Fusariosis has been described in patients with hematologic malignancies who are undergoing intensive cytotoxic chemotherapy or bone marrow transplantation. Numerous antifungal agents, alone or combined, have been prescribed to treat this life-threatening infection. None has been consistently effective. Our patient developed documented disseminated *Fusarium* infection during medullary aplasia associated with acute myeloid leukemia (AML), and voriconazole, a new antifungal triazole, was administered to the patient after therapy with amphotericin B and its liposomal formulation failed. This is the first published report of disseminated fusariosis in an immunocompromised host being successfully treated with voriconazole.

**Case Report.** A 65-year-old white man with AML was admitted in August 2000 (neutrophil count, 241 cells/mm³) for intensive intravenous induction chemotherapy (adriamycin, 65 mg per day [35 mg/m² per day] on days 1–3; Gs-chloronitrosurea, 148 mg per day [80 mg/m² per day] on day 1; and cytarabine, 190 mg per day [100 mg/m² per day] on days 1–10). On chemotherapy day 2, the patient became febrile (38–38.5°C). While receiving empiric therapy with tazocillin, ciprofloxacin, and gentamycin, his temperature returned to normal. On day 10 of chemotherapy, folliculitis appeared on the patient’s chest and back and disappeared 1 week later with no treatment change. From day 14 to day 41 of chemotherapy, no neutrophils were detected in samples obtained from the patient. On day 14, fever recurred, and ceftazidime and vancomycin therapy was prescribed. Severe mucositis prompted the addition of fluconazole (400 mg per day for 1 week) and metronidazole (500 mg t.i.d.) therapy. On day 18 of therapy, the patient’s fever rose to 40°C, and purpuric skin nodules appeared on the left palm and the right lower leg. Neutrophil recovery (239 neutrophils/mm³) occurred on day 42. Histologic examination of a specimen from a leg nodule showed signs of vasculitis, but findings of Gomori-Grocott, Zielhl, and periodic acid-Schiff stains were negative. However, direct mycological examination with Giemsa and methenamine silver stains detected filamentous fungus, and the culture of the skin biopsy specimen was positive for *Fusarium* species. Multiple routine and fungal blood cultures were negative for *Fusarium* species. Disseminated fusariosis with cutaneous manifestations was diagnosed using the criteria recommended by the International Society for Human and Animal Mycology [3]. The patient was initially treated on day 21 of therapy with amphotericin B (1 mg/kg, 60 mg per day) for 2 days, which was replaced with liposomal amphotericin B (Ambisome [Fujisawa Healthcare], 350 mg per day) until day 36 because of elevated creatinine clearance. The patient also received hematopoietic growth factors (granulocyte colony stimulating factor [G-CSF], 5 μg/kg per day on days 20–30). The skin lesions and fever persisted.

The reported efficacy of voriconazole against *Fusarium* in vitro [4] led us to try this new triazole in our patient’s therapy. Treatment with voriconazole was initiated on day 36 of therapy with the intravenous loading dose of 6 mg/kg (450 mg) b.i.d. and was followed by the maintenance dose of 4 mg/kg (300 mg) b.i.d. for 20 days. The patient became afebrile after 1 week, and all the skin lesions disappeared at that time. G-CSF was readministered on day 48. The switch to treatment with oral voriconazole (200 mg b.i.d. for 3 months) was made on day 56. Treatment with voriconazole was well tolerated and provided dramatic clinical improvement without relapse, despite...
the subsequent reinitiation of induction chemotherapy cycles on day 78 of therapy. In February 2003, the patient is still alive with no fusariosis, despite many other episodes of chemotherapy-induced medullary aplasia.

Discussion. Fusarium species are common soil saprophytes and plant pathogens that have emerged as opportunistic fungi in patients with neutropenia who have hematologic cancers and are undergoing intensive cytotoxic chemotherapy or bone marrow transplantation [5]. Fusarium represents a major complication for immunocompromised patients and is associated with high morbidity and mortality rates. Among this population, the incidence of invasive Fusarium species infections is second only to that of infections caused by Aspergillus species [6]. After the failure of amphotericin B therapy, we prescribed treatment with voriconazole, a new antifungal triazole, to a patient with documented disseminated Fusarium infection occurring during AML-associated medullary aplasia. Although some cases were described in an abstract [7], this is, to the best of our knowledge, the first published report of the efficacy of voriconazole therapy against human fusariosis in an immunocompromised host. Only 1 case of oculocutaneous fusariosis in an immunocompetent host successfully treated with voriconazole therapy has been published [8].

In our patient’s case, as in 55% of Fusarium infection cases [6], the disease was diagnosed on the basis of the findings of a mycological examination and a staining of a skin biopsy specimen; the results of histologic examination and blood cultures were not contributive to the diagnosis. Our patient’s clinical presentation of invasive fusariosis was similar to that described by Boutati and Anaissie [2] and was compatible with disseminated infection, with the skin lesions being considered metastases. Approximately 72% of immunocompromised patients with disseminated fusariosis have skin lesions [6], but Fusarium infection can involve any organ. Indeed, severe neutropenia, like that found in our patient, contributes to the high risk of developing skin lesions, and such lesions are often disseminated.

Strategies for treatment of fusariosis in the immunocompromised host are not yet well established. Amphotericin B and its liposomal formulation are the most useful systemic drugs and are considered reference standards, despite numerous therapeutic failures [2, 9]. We initially prescribed amphotericin B therapy, then ambisome therapy for 2 weeks, but neither treatment had any effect. Indeed, in the neutropenic host with fusariosis, a response to conventional or high doses of amphotericin B (1–2 mg/kg per day) is generally poor, and therefore an increase in neutrophil levels is considered essential to the cure of this infection; the patient may have a relapse if neutropenia recurs [1, 2]. In the study by Hennequin et al. [3], 31 patients received 9 different antifungal drug combinations, and none of the drug combinations was shown to be significantly more effective than the others.

Several published reports concur that Fusarium species, usually clinical isolates, are resistant to in vitro rifampicin, flucytosine (when administered alone), some triazoles (i.e., fluconazole, itraconazole), and amphotericin B (administered alone or combined with azithromycin or rifampicin) [5, 9, 10]. Resistance to flucytosine and fluconazole was practically universal. Only the 2 polyenes, amphotericin B (the most extensively studied drug) and natamycin, showed any significant in vitro activity. Notably, voriconazole exhibits potent in vitro wide-spectrum activity against clinically important fungal pathogens, including those resistant to fluconazole, itraconazole, or amphotericin B (such as Candida species, Aspergillus species, and Cryptococcus neoformans), and it is also active against less-common mold pathogens, including several species of Fusarium, Penicillium marneffei, and Scedosporium species [4, 11, 12].

In animal models of disseminated fusariosis, Guarro et al. [13] found no significant differences between the efficacy of amphotericin B when administered alone and its efficacy when combined with rifampicin or flucytosine (P > .5), even though these combinations are commonly used to treat severe invasive Fusarium infections. Even when the clinical isolates were susceptible to amphotericin B therapy in vitro, the correlation with the clinical response has been poor. Voriconazole therapy was also effective in animal models of systemic candidiasis; pulmonary and intracranial cryptococcosis; systemic and pulmonary aspergillosis; and aspergillus endocarditis [12].

Alternative therapeutic options against Fusarium could include the use of new triazoles such as voriconazole administered in combination with granulocyte transfusions [2]. Indeed, voriconazole therapy proved effective against disseminated fusariosis in our patient with neutropenia. Case reports also document successful treatment with voriconazole in immunocompromised hosts with chronic invasive aspergillosis and opportunistic Scedosporiosis [14]. Three large phase III trials have confirmed voriconazole’s status as a useful antifungal drug. These 3 studies have indicated that voriconazole therapy is at least as effective, and sometimes more so, than traditional therapies for severe fungal infections caused by organisms such as Candida species, Aspergillus species, or Scedosporium apiospermum [15–17]. Voriconazole is approved for the treatment of fusariosis in patients intolerant of or with infection refractory to other drugs. In data presented to the US Food and Drug Administration, 9 (43%) of the 21 patients with fusariosis achieved complete or partial responses with voriconazole therapy, which was prescribed on a compassionate-use basis [18].

Three distinct categories of adverse effects of voriconazole therapy have been reported: visual disturbances (~30% of patients), skin reactions (23–25%) [17, 19], and liver enzyme abnormalities (10%) [12]. It is not possible to delineate recommendations for voriconazole use on the basis of a single case, but its antifungal activity and favorable pharmacological...
properties, especially its infrequent and mild side effects, indicate a promising role for voriconazole therapy in combination with the administration of hematopoietic growth factors in treating *Fusarium* infections, and perhaps other fungal infections, in patients with hematologic malignancies.

**References**