Success of posaconazole therapy in a heart transplanted patient with *Alternaria infectoria* cutaneous infection

BLANDINE RAMMAERT*, CLAIRE AGUILAR*, MARIE-ELISABETH BOUGNOUX†, NICOLAS NOËL*, CAROLINE CHARLIER*, BLANDINE DENIS*, MARC LECUIT‡ & OLIVIER LORTHOLARY§

*Service des Maladies Infectieuses et Tropicales and †Unité de Parasitologie-Mycologie, Service de Microbiologie, Hôpital Necker-Enfants malades, Université Paris-Descartes, Sorbonne Paris Cité APHP, Centre d’Infectiologie Necker-Pasteur, Institut Imagine, Paris, ‡Groupe Microorganismes et barrières de l’hôte, and §Unité de Mycologie Moléculaire, Centre National de Référence Mycologie et Antifongiques, Institut Pasteur, Paris, France

Cutaneous *Alternaria* spp. infections occur mainly in immunosuppressed patients and itraconazole is considered as the drug of choice. We report the case of a 64-year-old heart transplanted female patient with multiple cutaneous lesions caused by *Alternaria infectoria*. Treatment with posaconazole resulted in complete recovery. Due to lower minimal inhibitory concentrations, better distribution and less drug interactions than with itraconazole, posaconazole may become the antifungal drug to consider in the management of cutaneous infections caused by *Alternaria* spp. in solid organ transplant recipients.

**Keywords** solid organ transplantation, triazoles, skin infectious diseases, phaeohyphomycosis

Introduction

The incidence of infection due to melanized fungi is increasing in humans, especially in the immunocompromised hosts who have received solid organ transplantation or in the hematological settings [1,2]. Unfortunately, no therapeutic guideline has as of yet been published. Based on *in vitro* data and a relatively low number of successfully treated patients, itraconazole has been advocated as first line therapy in a recent review [3], despite the fact that it presents major drug interactions, particularly with calcineurin inhibitors [4]. We report a case of skin infection caused by *Alternaria infectoria* successfully treated with posaconazole in a heart transplant recipient.

Case report

A 64-year-old woman farmer was admitted in June 2010 for skin lesions and pulmonary nodules. She had previously received a heart transplantation in 1998 for dilated cardiomyopathy. She experienced many episodes of graft rejection and was treated with corticosteroids, the latest treatment in December 2009. At the time of admission, her immunosuppressive regimen consisted of tacrolimus (7 mg/d), mycophenolate mofetil (2000 mg/d) and prednisone (7.5 mg/d). Her major underlying conditions were type II diabetes, which was poorly controlled with oral medication, chronic renal insufficiency with a creatinine clearance around 20 ml/min and monoclonal hypergammaglobulinemia with low residual gammaglobulins (2.4 g/l). Her skin lesions appeared in December 2009 in the context of pneumonia which was resistant to co-amoxiclav. The etiologic agent was identified as *Nocardia* spp. when recovered from bronchoalveolar lavage. She was treated with cotrimoxazole and ceftriaxone for six weeks, and once this therapy was discontinued, cutaneous biopsies were performed in January 2010. Histopathological analysis of a skin biopsy revealed granulomatous lesions with hyphae and rounded yeast-like structures without further
identification of the organism but no treatment was given. Six months later, the patient presented with recurrence of nocardiosis with pulmonary and cerebral involvement, and a sphenoidal sinus aspergilloma which was surgically resected. The skin lesions had also worsened and had become painful. On admission, the patient was found to have hyperglycemia (18 mmol/l). Cutaneous lesions were multiple, centimetric, budding, ulcerative and necrotic, distributed on toes, feet and anterior face of the left leg (Fig. 1). There was no evidence for osteomyelitis on X-ray imaging. New cutaneous biopsies were performed and histopathology revealed an irregular septated filamentous fungus (Fig. 2). Portions of the biopsy material cultured on Sabouraud chloramphenicol gentamicin agar yielded yellowish colonies after three-day incubation at 30°C (Fig. 3). Unfortunately, the lack of conidial formation did not allow identification of this filamentous fungus. The strain was identified by molecular methods, i.e., the complete ITS1-5.8S-ITS2 ribosomal locus was amplified with the fungal universal primer pair ITS 1/ITS 4, and both strands of PCR products were sequenced. Sequence comparison analysis using the GenBank database (National Center for Biotechnology Information) demonstrated 99% identity over 466 bp with the Lewia cf. infectoria CBS120150 sequence (accession no FJ214865), teleomorph of A. infectoria [5].

Itraconazole treatment was initiated for three weeks but no improvement was observed in the cutaneous lesions. Minimal inhibitory concentrations (MICs) of the following antifungals against this isolate were found through the E-test to be: itraconazole MIC, 1 μg/ml, voriconazole MIC 32 μg/ml, and posaconazole MIC 0.0064 μg/ml. The patient was started on posaconazole 400 mg b.i.d, with the dosage increased to 400 mg t.i.d. because the trough reading was 0.94 mg/l. Tolerance was excellent, in particular no QT interval prolongation, and co-administered immunosuppressive regimen was adapted with tapering tacrolimus dose (3 mg/d) because of azole interaction. Local treatment in the form of silver nitrate application on budding lesions was also administered. Diabetes mellitus was controlled with the introduction of subcutaneous insulin injections. Cutaneous lesions improved within a month of posaconazole therapy, with complete healing in four months. The patient is still under treatment with posaconazole 12 months after therapy initiation because of profound immunodepression related to chronic graft rejection.

Discussion

This case report demonstrates the potent in vitro and in vivo activity of posaconazole against Alternaria spp., a derma-
Posaconazole have erratic oral absorption depending on gastric pH. Nevertheless, posaconazole has a broad body tissues distribution. A recent randomized trial evaluated posaconazole concentrations in the skin of 30 healthy subjects. After oral administration of 400 mg b.i.d., 10 minutes after finishing a high-fat meal, posaconazole levels in the skin were similar to plasma levels on day 8 and achieved several fold higher concentrations than the MIC\textsubscript{90} value of 0.25 μg/ml [11]. Posaconazole use is also safe for prolonged treatment of more than six months [12]. In addition, phaeohyphomycetes susceptibility to posaconazole is greater than that of itraconazole. Of the 39 phaeohyphomycetes recovered from patients with cancer who were studied recently, all isolates had MICs for posaconazole ≤ 1.0 μg/ml [1]. In another study of Cladophialophora spp., all the 42 strains exhibited low posaconazole MICs [13]. Posaconazole was also used with success in a case of cerebral phaeohyphomycosis caused by Rhinocladiella mackenziei, but susceptibility testing was not performed [14]. For A. infectoria, posaconazole MIC is generally lower than that of itraconazole, ranging from 0.063–0.125 μg/ml [15].

In conclusion, posaconazole represents an attractive alternative to itraconazole for the management of cutaneous A. infectoria infection, particularly in transplanted patients.

Acknowledgements

We are grateful to Dr Ngoc Tram To from the Cardiology Unit at Marie Lannelongue hospital (Le Plessis Robinson, France) for the patient’s follow-up.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

References

Success of posaconazole in a patient with A. infectoria infection


This paper was first published online on Early Online on 5 December 2011.