Medical Mycology Case Reports 27 (2020) 42–43

Contents lists available at ScienceDirect

Medical Mycology Case Reports

journal homepage: www.elsevier.com/locate/mmcr

HIV-associated disseminated histoplasmosis successfully treated with isavuconazole consolidation therapy

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ARTICLE INFO

Keywords:
Histoplasmosis
Isavuconazole
Itraconazole
HIV
Histoplasma capsulatum

ABSTRACT

A 30-year-old man with advanced HIV and disseminated histoplasmosis deteriorated after stepping down from intravenous liposomal amphotericin B to itraconazole.

Therapeutic levels of itraconazole and posaconazole were not achieved, therefore liposomal amphotericin B was reintroduced. Stepdown treatment was switched to oral isavuconazole; since then the patient has remained well.

1. Introduction

Disseminated histoplasmosis, an infection caused by dimorphic fungus *Histoplasma capsulatum*, is well described in patients with advanced HIV, and it carries a high mortality [1]. Standard therapy is with intravenous liposomal amphotericin B (LAmB), followed by oral itraconazole [2,3], however itraconazole has variable patient-to-patient pharmacokinetics, and its inadequate plasma concentrations can lead to subtherapeutic drug levels and treatment failure [4]. Isavuconazole is a newer azole antifungal that has in vitro activity against *H. capsulatum* [5]; the evidence for its clinical use to treated disseminated histoplasmosis is however scarce. Here we present a case of disseminated histoplasmosis successfully treated with isavuconazole consolidation therapy.

2. Case

A 30-year-old man, born and raised in Ghana but recently moved to the UK, presented with a 2-week history of fever, cough, diarrhoea, and weight loss. He had been recently diagnosed with HIV infection but had not yet started treatment. HIV viral load was 1.5 million copies/mL, and CD4 count was 20/μL (2%). On admission (day 0), he was pyrexial with hepatosplenomegaly and oral candidiasis; blood tests showed a normocytic anaemia, neutrophilia, eGFR > 90 mL/min, AST 120 U/L, ALT 88 U/L, bilirubin 10 μmol/L, CRP 112 μmol/L.

CT scan of the thorax, abdomen and pelvis revealed clear lung fields, mild cardiomegaly, and hepatosplenomegaly. There was no significant lymphadenopathy. β-D-glucan level was elevated at 146 pg/mL (url: 80 pg/mL) and serum galactomannan antigen index was 11.187.

A liver biopsy was performed; Grocott staining showed small spherical organism consistent with *Histoplasma*. Nuclear ribosomal repeat region sequencing was positive for *H. capsulatum* fungal 18s rRNA gene. A bone marrow biopsy revealed haemophagocytosis and yeasts. Additionally, *H. capsulatum* was isolated from a sputum culture.

MRI brain and CSF analysis showed no evidence of CNS involvement. *Histoplasma* urinary antigen was positive, although testing is not routinely available in the UK, therefore the result was obtained after the diagnosis had been obtained by PCR of the liver biopsy.

A diagnosis of disseminated histoplasmosis in the context of advanced HIV was made. Treatment with intravenous LAmB (3 mg/kg once daily) was commenced on day 22, followed a week later by antiretroviral therapy with emtricitabine, tenofovir disoproxil and dolutegravir. The patient had a marked clinical improvement, with resolution of pyrexia and decrease of inflammatory markers.

On day 39, LAmB was switched to oral itraconazole capsules, 200mg twice daily.

The patient was followed up as an outpatient on a weekly basis. He reported good compliance with both antiretrovirals and itraconazole. Repeated HIV viral load was undetectable, and CD4 count had increased to 50/μL.

On week 10, he was found to be pyrexial at 39.6 °C, therefore he was re-admitted to hospital. Plasma itraconazole concentration was 0.2 mg/L (reference range 1–2 mg/L). Due to presumed relapse of

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https://doi.org/10.1016/j.mmcr.2019.12.013
Received 18 December 2019; Accepted 19 December 2019
Available online 20 December 2019

histoplasmosis (as no other cause of fever was found), intravenous LAmB was restarted at the same dose alongside oral itraconazole, this time in liquid suspension given the low drug levels with capsules. Despite directly observed treatment as an inpatient, trough itraconazole levels remained subtherapeutic.

Itraconazole was switched to posaconazole on week 18 (liquid suspension, 400 mg once daily), alongside LAmB. Plasma trough posaconazole levels, however, were also subtherapeutic, at 0.09 mg/L. Voriconazole was avoided due to concerns regarding drug interactions and toxicity.

Oral isavuconazole was therefore introduced in month 7 (loading dose 200 mg 8-hourly for 48 hours, followed by 200mg once daily) alongside LAmB. An isavuconazole plasma trough level after one week of treatment was 1.72 μg/mL, and later consistently > 1.6 μg/mL.

The patient significantly improved with resolution of fever and was able to continue on isavuconazole monotherapy and has since made a complete clinical recovery. He remains well on isavuconazole therapy one year later.

3. Discussion

This patient was from Ghana, where the burden of histoplasmosis is unknown, but likely to be grossly underestimated due to lack of diagnostics. However, there are 12 case reports of histoplasmosis from Ghana over 60 years, mostly associated with HIV [6].

Treatment is usually with oral itraconazole after amphotericin-based therapy.

Isavuconazole is a newer antifungal triazole, used for treatment of both invasive aspergillosis and mucormycosis [7]. It also has in vitro activity against *H. capsulatum* [5], reliable pharmacokinetics and relatively few drug interactions, making it an attractive agent for use in this context. Additionally, it is unique amongst azole antifungals in that it shortens rather than prolongs the QT interval, which can preclude use of azoles in some patients [8].

To date, there has been very limited experience with isavuconazole to treat disseminated histoplasmosis. In the VITAL study [9], seven patients with histoplasmosis were treated with primary or salvage isavuconazole therapy. Out of the four with disseminated disease, half had treatment success, one had a partial success, and another had progression. Isavuconazole was also used successfully in a case of *Histoplasma* endocarditis [10] and in a case of oesophageal histoplasmosis in the context of advanced HIV infection [11].

We are not aware of any previously reported cases treated with isavuconazole as a consolidation treatment after induction with LAmB.

As there is high interpersonal variability in itraconazole and posaconazole pharmacokinetics, it is strongly suggested to routinely perform therapeutic drug monitoring (TDM) after starting treatment [4]. Additionally, their absorptions are highly variable and are not consistent between drug formulations. As isavuconazole has reliable more pharmacokinetics, its TDM is not routinely indicated [4], but may be required in complex cases, or in renal impairment. The Public Health England Mycology Reference Laboratory refers to 2.0–4.0 μg/mL as the normal range for isavuconazole. However, a clinically relevant therapeutic range has yet to be established, as no drug level threshold has been linked to outcome [12]. In our case, measured isavuconazole levels were slightly below this range.

This case describes successful consolidation treatment of disseminated histoplasmosis with isavuconazole, in a person living with HIV and in whom therapeutic drug levels were not achievable with itraconazole or posaconazole. This suggests that isavuconazole is a viable therapeutic option as an alternative to itraconazole and requires further evaluation as consolidation therapy in the treatment of histoplasmosis and other invasive fungal infections.

Declaration of competing interest

There are none.

Erica Pool is funded by a National Institute for Health Research Academic Clinical Fellowship. The views expressed are those of the author(s) and not necessarily those of the National Health Service (NHS), the NIHR or the Department of Health.

Acknowledgements

We are thankful to Dr Elizabeth Johnson (PHE Mycology Reference Laboratory), Joyce Mahungu and Dr Jonathan Ainsworth (NMUH Alexander Pringle Centre), Dr Mariyam Mirfenderesky and Dr Nehal Draz (NMUH Microbiology) for the extremely helpful advice.

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