Clinical Infection in Practice xxx (xxxx) xxx

Contents lists available at ScienceDirect

Clinical Infection in Practice

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

Case Reports and Series

Cutaneous phototoxic reaction to intravenous micafungin in the outpatient setting: A case report

Arthur Price [a], Thomas C. Morris [b], Helena A. White [b], Ryan A. Hamilton [c,d,*]

[a] Department of Immunology, University Hospitals of Leicester NHS Trust, United Kingdom
[b] Department of Infection and HIV Medicine, University Hospitals of Leicester NHS Trust, United Kingdom
[c] Pharmacy Department, University Hospitals of Leicester NHS Trust, Leicester, United Kingdom
[d] Leicester School of Pharmacy, De Montfort University, Leicester, United Kingdom

ARTICLE INFO

Article history:
Received 29 July 2020
Received in revised form 4 December 2020
Accepted 8 December 2020
Available online xxxx

Keywords:
Micafungin
Phototoxicity
OPAT
Chronic mucocutaneous candidiasis
STAT1
Case report

ABSTRACT

Background: Signal Transducer and Activator of Transcription 1 (STAT1) Gain of Function (GoF) mutations can predispose to chronic mucocutaneous candidiasis (CMC). Long term therapy with oral azole antifungals can result in resistance and the need to treat with alternatives such as echinocandins.
Case Report: A pan-azole-resistant *Candida albicans* was isolated from a mouth swab from a 39-year-old woman with lifelong CMC. Her condition warranted systemic treatment and this was achieved through daily infusions of micafungin, which the patient self-administered at home within the OPAT (Outpatient Parenteral Antimicrobial Therapy) service. The patient experienced a good and rapid clinical response. On day 18 of treatment the patient developed an itchy rash and presented back to our hospital on day 22. A diagnosis of phototoxic skin reaction, secondary to micafungin, was established through clinical history, signs, and investigations.
Results: Micafungin was withdrawn and the phototoxic reaction resolved without further intervention. The patient was maintained on amphotericin oral lozenges.
Conclusion: More research into the phototoxic potential of micafungin and its metabolites is needed but clinicians should remain aware of the potential of phototoxicity in individuals treated in outpatient and OPAT settings.

Background

Autosomal dominant Signal Transducer and Activator of Transcription 1 (STAT1) Gain of Function (GoF) mutations are recognised as the most common monogenic cause of chronic mucocutaneous candidiasis (CMC) since their identification in 2011. STAT1 is a second messenger within the JAK-STAT pathway and in GoF mutations there is increased STAT1 phosphorylation which drives a skewed immune response (Zheng et al., 2015). They have a wide clinical spectrum from pure mucocutaneous candidiasis with or without autoimmune disease through to a severe immunodeficiency with enteropathy. Increased candidiasis, which is often difficult to treat, is likely due to impaired Th17 responses (Firinu et al., 2011).

Oral azole antifungals, such as fluconazole, itraconazole, and voriconazole are generally recommended as the first-line agents for non-genital mucocutaneous candidiasis and CMC (Pappas et al., 2004). Azole-resistant isolates of Candida have been observed in patients with CMC secondary to STAT1-GoF treated with prolonged courses of tri-azole antifungals (Humbert et al., 2018). In the UK, micafungin is licensed in adults for i) treatment of invasive candidiasis, ii) treatment of oesophageal candidiasis in patients for whom IV therapy is appropriate, and iii) prophylaxis against Candida infection in those undergoing allogeneic haematopoietic stem cell transplantation or who are expected to have neutropenia for 10 days or more (MHRA, 2019). Therefore, micafungin would be a reasonable second-line option in cases of azole-resistance or other contraindications in patients with CMC. Micafungin is a semi-synthetic lipopeptide belonging to the echinocandin class that selectively inhibits the formation of 1,3-β-D-glucan, which is a vital component of the fungal cell-wall, thus resulting in cell lysis (Wasmann et al., 2017). Micafungin distributes widely into tissues and achieves therapeutic concentrations in skin-structures, lung tissue and peritoneal fluid, but penetration into the CSF is limited (Felton et al., 2014; Yamada et al., 2011).

* Corresponding author at: Leicester School of Pharmacy, De Montfort University, Leicester LE2 7GZ, United Kingdom.
E-mail address: ryan.hamilton@dmu.ac.uk (R.A. Hamilton).

https://doi.org/10.1016/j.clinpr.2020.100061
2590-1702/

Please cite this article as: A. Price, T.C. Morris, H.A. White et al., Cutaneous phototoxic reaction to intravenous micafungin in the outpatient setting: A case report, Clinical Infection in Practice, https://doi.org/10.1016/j.clinpr.2020.100061

Here we present the case of a 39-year-old woman with lifelong CMC who has a novel pathogenic mutation in STAT1 and experienced phototoxicity during micafungin treatment for azole-resistant CMC.

Case report

Before referral to immunology, the patient had experienced persistent oral candidiasis for many years, managed in primary care with repeated courses of fluconazole and itraconazole. The patient's mother had the same symptoms, but died of *'throat'* cancer aged 53. The patient's 7-year-old daughter has the same mutation but remains asymptomatic at the time of this report. Her dentition was very poor due to dental phobia and smoking tobacco. Repeated HIV testing was negative and she had no other symptoms attributable to her STAT1-GoF; no inflammatory bowel disease, negative autoantibodies to endocrine organs, negative ANA, normal total immunoglobulins and normal T, NK and B cell numbers.

On diagnosis of STAT1-GoF, mouth swabs in September 2018 and June 2019 isolated *Candida albicans* with pan-azole resistance but susceptibility to amphotericin, echinocandins and flucytosine. Severe oral discomfort from oral candidiasis and a painful swallow, suggesting oesophageal involvement, led to a referral to the Outpatient Parenteral Antimicrobial Therapy (OPAT) service for consideration of parenteral antifungals.

Intravenous micafungin 150 mg once daily, as per the UK license for managing oesophageal candidiasis, for an initial period of fourteen days was commenced in April 2019. After training by the OPAT specialist nurses, the patient self-administered micafungin at home via a midline. By day 8 her symptoms were much improved, with some mild residual soreness of the throat. On examination the mouth was still slightly inflamed but only one to two white plaques in the mouth were visible. On day 15 there was no odynophagia and the mouth appeared clear. On advice from regional experts, treatment was extended by seven further days to reduce the risk of early relapse, particularly given the lack of oral alternatives.

On day 22, the patient attended routine end-of-treatment follow-up with a rash. This had started four days' previously as uncomfortable non-itchy "bumps". The weather having been warm and bright, she had been wearing a t-shirt with thin shoulder-straps and trousers ending at her mid-calf. The rash was only evident on skin-exposed areas over her upper chest, shoulders, arms and ankles. There was sparing of the face, which the patient attributed to her makeup providing high levels of UV protection. At review, the rash had progressed to a confluent erythematous rash and the skin appeared slightly oedematous with mild pitting over the distal tibiae. Eosinophil counts were not raised and hepatic and renal function tests were normal.

Micafungin was immediately stopped. The patient did not require hospital admission and the rash resolved spontaneously after a few days. She has not had micafungin since, although a further course is planned around the time of elective dental clearance in 2020, when she will be advised to avoid exposure to direct sunlight where possible, apply high sun protection factor (SPF) cream to exposed areas, and ensure the micafungin infusion is protected from light. The patient has been maintained on amphotericin lozenges for oral symptoms, and terbinafine for *Trychophyton* isolated from nail clippings.

Discussion

This is the first case in the published literature to describe a phototoxic skin reaction in an individual taking micafungin, and is also the first reported case of such a reaction in an individual with STAT1-GoF mutation. Although our centre does undertake phototoxicity testing, the case history and clear demarcation from clothing and high-SPF makeup, and absence of other identifiable causes suggest this phototoxic reaction was driven through exposure to sunlight, rather than a generalised dermatological drug-reaction to micafungin. The development of this reaction over a number of days, its symptomatic description by the patient, and the clinical findings also make differential causes such as sunburn, heat rash, and generalised dermatological drug-reaction unlikely causes. While skin reactions such as rashes, erythema, erythema multiforme, and Stevens-Johnson Syndrome / Toxic Epidermal Necrolysis (SJS/TEN) are highlighted within product literature (MHRA, 2019), this is the first case in the medical and scientific literature of a phototoxic skin reaction to this drug, and is the first case of this reaction to be reported to the UK's Medicines and Healthcare products Regulatory Agency (MHRA) Yellow Card Scheme. Lack of reports of phototoxicity secondary to micafungin may be due to it predominately being used within hospital settings, where exposure to sunlight is less likely. Our patient was ambulatory and self-administering micafungin within the OPAT service, which allowed her to remain at home and live a near normal life and enjoy being outside in the warm and bright weather at the time.

Absorption of UV-photons by drug-molecules can result in structural changes, photolysis, and generation of reactive oxygen species, which can cause dermal toxicity (Kim et al., 2015). Stability studies undertaken during the micafungin licensing process demonstrated up to 12.2% loss under a 3000 lx lamp, resulting in advice within the product literature to protect the product and infusions from UV light (CHMP, 2008). Subsequent studies identified approximately eleven break-down products that can arise from UV-photolysis, hydrolysis, oxidation, and biologic metabolism of micafungin (Zhu et al., 2013). Micafungin distributes widely into most tissues (V_d 0.2 L/kg) and achieves therapeutic concentrations in skin-structures (T/P ratio $\sim$ 0.46) (Yamada et al., 2011). Within the skin and skin-structures it is likely to be exposed to UV-light, within an aqueous and oxygenated environment, enabling photolysis and the generation of a range of secondary break-down molecules. The antifungal effects of some of these metabolites have been demonstrated (Ikeda et al., 2002) and standard pharmacokinetic parameters have been defined in adults and children for the two major metabolites M1 and M2 (Tabata et al., 2006; Azuma et al., 2002). However, the phototoxic potential of micafungin or its metabolites has not been specifically determined, even though the majority of these molecules contain chromophores. This case highlights the need to further characterise the metabolites of micafungin and determine their potential for phototoxicity.

It remains unclear whether STAT1-GoF or CMC can predispose to photosensitivity, with only one other instance of photosensitivity of the skin and genital mucosa reported in a 3-month-old baby with CMC but who was also ANA positive (Liu, 2013). Considering how rare these conditions are and the infrequent use of micafungin in the outpatient setting, an interplay between STAT1-Gof, CMC and micafungin inducing phototoxicity cannot be completely excluded.

Conclusion

This is the first reported case of phototoxicity due to intravenous micafungin therapy. However, the ability of micafungin and its metabolites to induce such phototoxicity requires further investigation. Similarly, the role of STAT1-GoF and CMC in photosensitivity also requires further research. Increasingly, patients are receiving intravenous antimicrobials, including micafungin, in

their own homes (Durojaiye et al., 2019), so those administering this drug must be reminded to protect the infusion from light and clinicians should remain aware of the potential for phototoxicity. If future research proves micafungin can precipitate phototoxic reactions it will be necessary to advise patients to protect themselves from sunlight by avoiding exposure where possible or using high SPF creams.

Funding

No funding received. This study was carried out as part of routine work.

Ethical approval

Informed consent to publish this case was obtained from the patient. No images or photographs of the reaction were obtained by the clinicians or the patient.

Transparency declarations

AP, TCM and HAW have no conflict of interest. RH has previously received educational grants from Astellas Pharma Ltd. (manufacturer of Mycamine, micafungin). No external organisations (including Astellas) were involved in the management of this case or the production of this report. There are no other conflicts of interest.

CRediT authorship contribution statement

Arthur Price: Writing - original draft, Writing - review & editing, Investigation. **Thomas C. Morris:** Writing - original draft, Writing - review & editing, Investigation. **Helena A. White:** Writing - original draft, Writing - review & editing, Investigation. **Ryan A. Hamilton:** Writing - original draft, Writing - review & editing, Project administration.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: AP, TCM and HAW have no conflict of interest. RH has previously received educational grants from Astellas Pharma Ltd. (manufacturer of Mycamine, micafungin). No external organisations (including Astellas) were involved in the management of this case or the production of this report. There are no other conflicts of interest.

References

Azuma, J., Nakahara, K., Kagayama, A., et al., 2002. Pharmacokinetic study of micagungin. Japanese J. Chemother. 50, 155–184. https://doi.org/10.11250/chemotherapy1995.50.Supplement1_155.

CHMP. Mycamine, INN-micafungin. 2008. http://www.emea.europa.eu (accessed 30 Jan 2020).

Durojaiye, O.C., Cartwright, K., Ntziora, F., 2019. Outpatient parenteral antimicrobial therapy (OPAT) in the UK: a cross-sectional survey of acute hospital trusts and health boards. Diagn. Microbiol. Infect. Dis. 93, 58–62. https://doi.org/10.1016/j.diagmicrobio.2018.07.013.

Felton, T., Troke, P.F., Hope, W.W., 2014. Tissue Penetration of Antifungal Agents. Published Online First: 2014. https://doi.org/10.1128/CMR.00046-13.

Firinu, D., Massidda, O., Lorrai, M.M., et al., 2011. Successful treatment of chronic mucocutaneous candidiasis caused by azole-resistant Candida albicans with posaconazole. Clin. Dev. Immunol. 2011. https://doi.org/10.1155/2011/283239.

Humbert, L., Cornu, M., Proust-Lemoine, E., et al., 2018. Chronic mucocutaneous candidiasis in autoimmune polyendocrine syndrome type 1. Front. Immunol. 9, 2570. https://doi.org/10.3389/fimmu.2018.02570.

Ikeda, F., Otomo, K., Wakai, Y., et al., 2002. Antifungal activities of the Ml, M 2 and M 5 metabolites of micafungin. Japanese J. Chemother. 50, 54–57. https://doi.org/10.11250/chemotherapy1995.50.Supplement1_54.

Kim, K., Park, H., Lim, K.-M., 2015. Phototoxicity: its mechanism and animal alternative test methods. Toxicol. Res. 31, 97. https://doi.org/10.5487/TR.2015.31.2.097.

Liu, Luyan, 2013. Identification and characterization of molecular genetic bases responsible for the predisposition to chronic mucocutaneous candidiasis in humans. Human health and pathology. Université René Descartes - Paris V, 2013. English. ffNNT: 2013PA05T009ff. fftel-00838931f (Available online: https://tel.archives-ouvertes.fr/tel-00838931).

MHRA. Micafungin Teva 100 mg Powder for Solution for Infusion - Summary of Product Characteristics. 2019. https://mhraproductsprod.blob.core.windows.net/docs-20200316/48f814565534c9898099f46fa39b67058d7572f9 (accessed 17 Mar 2020).

Pappas, P.G., Rex, J.H., Sobel, J.D., et al., 2004. Guidelines for treatment of candidiasis. Clin. Infect. Dis. 38, 161–189. https://doi.org/10.1086/380796.

Tabata, K., Katashima, M., Kawamura, A., et al., 2006. Linear Pharmacokinetics of Micafungin and Its Active Metabolites in Japanese Pediatric Patients with Fungal Infections.

Wasmann, R.E., Muilwijk, E.W., Burger, D.M., et al., 2017. Clinical pharmacokinetics and pharmacodynamics of micafungin. Clin. Pharmacokinet. 57. https://doi.org/10.1007/s40262-017-0578-5.

Yamada, N., Kumada, K., Kishino, S., et al., 2011. Distribution of micafungin in the tissue fluids of patients with invasive fungal infections. J. Infect. Chemother. 17, 731–734. https://doi.org/10.1007/s10156-011-0240-3.

Zheng, J., van de Veerdonk, F.L., Crossland, K.L., et al., 2015. Gain-of-function STAT1 mutations impair STAT3 activity in patients with chronic mucocutaneous candidiasis (CMC). Eur. J. Immunol. 45, 2834–2846. https://doi.org/10.1002/eji.201445344.

Zhu, S., Meng, X., Su, X., et al., 2013. Development and validation of a stability-indicating high performance liquid chromatographic (HPLC) method for the determination of related substances of micafungin sodium in drug substances. Int. J. Mol. Sci. 14, 14. https://doi.org/10.3390/ijms141121202.