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Micafungin use in a UK tertiary referral hospital

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ABSTRACT

Objectives: Here we sought to describe the real-life usage of micafungin in a UK tertiary referral hospital.
Methods: A prospective, non-interventional, observational surveillance study was performed in a large teaching hospital do we need 'in a large teaching hospital' now since we say 'UK tertiary hospital' above?.
Results: Micafungin was commenced in 174 courses involving 148 patients to treat invasive candidiasis and candidaemia (132 courses) and aspergillosis in situations where alternatives such as voriconazole or liposomal amphotericin B could not be used (42 courses). Fungal infection was defined as proven as per European Organization for Research and Treatment of Cancer/Mycoses Study Group (EORTC/MSG) guidelines in 84 courses (48.3%). Micafungin was well tolerated; 10 patients (6.8%) developed a rise in alanine aminotransferase (ALT) and only 1 patient stopped therapy due to this. Therapy was rationalised to fluconazole in 77 courses (44.3%). There were no differences in intensive care unit admission or deaths when comparing all 174 courses where patients received micafungin for *Aspergillus* and *Candida* infection, respectively [49% vs. 42% ($P=0.82$) and 24% vs. 15% ($P=0.186$)]. One patient developed disseminated mucormycosis and four patients had recurrent candidaemia (attributed to poor source control) while receiving micafungin.
Conclusions: Micafungin was clinically effective for the treatment of invasive *Candida* and *Aspergillus* infections, and usage did not increase the risk of liver dysfunction even in patients with abnormal ALT at baseline.

1. Introduction

Micafungin (Mycamine®; Astellas Pharma Europe B.V., Leiderdorp, Netherlands) is a member of the echinocandin class of antifungal agents together with caspofungin and anidulafungin. It is licensed for use both in adults and children including neonates. Echinocandins target the fungal cell wall by selectively inhibiting the synthesis of 1,3-β-D-glucan, giving them a favourable side-effect profile [1]. Of note, however, is the warning that micafungin can potentially cause life-threatening hepatotoxicity. Micafungin has potent in vitro and in vivo activity against all major *Candida* spp. and *Aspergillus* spp. as well as less common pathogens such as *Paecilomyces* spp. and *Penicillium* spp. However, it has no activity against *Cryptococcus* spp. and members of the order Mucorales [1,2].

Micafungin is approved for the treatment of candidaemia, invasive candidiasis and oesophageal candidiasis [where intravenous (i.v.) therapy is appropriate] and prophylaxis of *Candida* infection in patients undergoing allogeneic haematopoietic stem cell transplantation or who are expected to have neutropenia for ≥10 days. Whilst micafungin is not licensed for treating infections due to *Aspergillus* spp. in Europe, there is evidence of its use, particularly in Japan [2]. Of note, however, is that echinocandins are not regarded as first-line therapy for invasive aspergillosis [3].

In the UK, Cambridge University Hospitals (CUH) NHS Foundation Trust introduced micafungin in April 2013 as the main echinocandin for the Trust. New revised guidelines were also launched accordingly. Here we sought to describe the real-life usage conditions of micafungin in our hospitals in adults and children, including reasons for the prescription, therapeutic scheme and treatment duration, and characteristics of the patients as well as to evaluate the patient response to treatment and its tolerability, particularly with regard to hepatic function.

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2. Methodology

A prospective, non-interventional, observational surveillance study of all patients (including children and neonates) commencing micafungin between 1 January 2014 and 31 December 2015 in a UK tertiary referral hospital was undertaken as part of the antifungal stewardship programme [4].

2.1. Setting

CUH NHS Foundation Trust is a tertiary referral hospital with ca. 1200 beds and ca. 70 000 in-patient episodes per year. It offers a number of specialist services including organ transplantation (liver, kidney, intestine and pancreas), haematology/oncology (including stem cell transplantation), infectious diseases, hepatology/hepatic-pancreatico-biliary (HPB) surgery, neurosurgery and intensive care (including neonatal, paediatric, neurocritical care and general adult) facilities.

2.2. Definitions

Courses were defined as one course of therapy, and one patient could have one or several courses. Treatment for a community-onset infection was defined as treatment commencing within 48 h of admission if the patient was not transferred from another hospital, whereas treatment of a healthcare-associated infection was defined as treatment occurring within 48 h of hospital admission in a patient who had previously been admitted to hospital in the preceding year or was admitted from a nursing/residential home. Treatment of a hospital-onset infection was defined as treatment commencing after this period. European Organization for Research and Treatment of Cancer/Mycoses Study Group (EORTC/MSG) definitions were used to characterise the reason for therapy as proven, probable or possible, and empirical or prophylaxis [5].

2.3. Variables

Demographic data, clinical details and antimicrobial history were obtained from laboratory and microbiology records and medical, nursing and pharmacy notes as well as the patient administration system.

2.4. Microbiology

Blood cultures were processed using a BacT/ALERT® 3D system (bioMérieux, Marcy-l'Étoile, France). Yeast identification and susceptibility testing were performed using VITEK®2 (bioMérieux). Bronchoalveolar lavage (BAL) and/or serum galactomannan assay was performed using a Bio-Rad platform (Bio-Rad, Hercules, CA). *Aspergillus* PCR (BAL and plasma) was performed at the Bristol Mycology Reference Laboratory (from 1 January 2014 until 30 April 2015).

2.5. Treatment algorithms

Micafungin 100 mg once daily was used for the treatment of invasive candidiasis and candidaemia. This dose was also used as prophylaxis when *Aspergillus* was suspected when patients were unable to tolerate the usual regimens (e.g. in transplant and haematology patients). A dose of 150 mg once daily was used for the treatment of oesophageal candidiasis and invasive aspergillosis. Micafungin was only given for prophylaxis or treatment of infections due to *Aspergillus* when there was thought to be no alternative formulary options [i.e. the patient was intolerant to voriconazole owing to side effects or drug–drug interactions or was intolerant of liposomal amphotericin B (L-AmB)]. Children received appropriate weight-based dosing according to the summary of product characteristics. Liver function test data, including alanine aminotransferase (ALT), were collected weekly during treatment.

2.6. Statistical analysis

Analyses are largely descriptive and were performed on all data recorded in the case report form. Quantitative variables were described by the number and percentage. Data were frequently skewed and the median and interquartile range (IQR) are provided. Differences in proportions were compared using the χ^2 test, and continuous variables were compared using the Mann–Whitney *U*-test. Logistic regression was used to calculate the odds ratio (OR) of binary outcomes. Kaplan–Meier plots were generated to compare the time to peak ALT and to ALT normalisation between those whose baseline ALT was normal or abnormal, which are characterised using a hazard ratio from a Mantel–Cox log-rank test. Data were analysed in Stata Statistical Software: Release 14 (StataCorp LP, College Station, TX) and GraphPad Prism (GraphPad Software Inc., La Jolla, CA). Statistical significance was determined by a *P*-value of <0.05.

2.7. Ethical approval

Ethical approval was sought and obtained from the CUH audit department as a service evaluation. This study was requested by the Joint Drug & Therapeutic Committee to ensure appropriate use and to assess tolerability. Patient management was not affected by the study and all data were held in an anonymous format.

3. Results

Micafungin was commenced for 174 courses in 148 patients, including 135 adults and 13 children aged <18 years (10 of whom were under paediatric oncology care, 2 of whom were neonates and 1 was under general paediatrics).

Of the 148 patients, 74 (50.0%) were female and 58.1% had a fatal underlying disease. One patient received five courses of micafungin (for biopsy-proven oesophagitis due to an azole-resistant *Candida albicans*), one patient received four courses of micafungin (for candidaemias due *Candida krusei* and *Candida glabrata*, all susceptible to echinocandins but with poor source control), two patients received three courses of micafungin (again for recurrent candidaemias due to echinocandin-susceptible strains but without source control) and 15 patients received two courses.

The majority of patients (89%) had central venous access, with a large number (42.6%) receiving total parenteral nutrition. Patients were immunosuppressed with haematological malignancy (26.4%) or solid organ transplant (20%). Neutropenia was present in 24 patients (16.2%) for a median duration of 13 days (IQR 8–15 days). Baseline patient demographics are shown in Table 1. Of the 174 courses, micafungin was initiated for *Candida* infection in 132 courses [53 candidaemia (30.5%), 69 invasive candidiasis (39.7%) and 10 oesophageal candidiasis (5.7%)] and *Aspergillus* in 42 courses [39 invasive aspergillosis (22.4%), 2 sinusitis (1.1%) and 1 aspergilloma (0.6%)]. Micafungin was given empirically for fungaemia but subsequently grew *Cryptococcus neoformans* in one course.

Fungal infection was proven as per EORTC/MSG guidelines in 84 courses (48.3%). Probable and possible fungal infection was diagnosed in 17 (9.8%) and 59 (33.9%) courses, respectively. Micafungin was used as prophylaxis for 14 courses (8.0%). The most common fungal infection confirmed by culture was *Candida* spp. isolated in 91 episodes (52.3%), followed by *Aspergillus* spp. in 8