The activity of micafungin against clinical isolates of non-\textit{albicans} Candida spp.

\textbf{Anna Biernasiuk*\textsuperscript{1}, Ewelina Dobiecka\textsuperscript{1}, Grazyna Zdzienicka\textsuperscript{2}, Anna Malm\textsuperscript{3}}

\textsuperscript{1}Department of Pharmaceutical Microbiology, Medical University of Lublin, Chodzki 1, 20-093 Lublin, Poland
\textsuperscript{2}Department of Diagnostics Microbiology, Independent Public Teaching Hospital No 1, Staszica 16, 20-081 Lublin, Poland

\textbf{ARTICLE INFO}

Received 02 March 2015
Accepted 12 March 2015

\textbf{Keywords:}
micafungin, non-\textit{albicans} Candida spp., E-test, minimal inhibitory concentration (MIC).

\textbf{ABSTRACT}

Infections caused by non-\textit{albicans} Candida spp. are an important medical problem in people from risk groups, \textit{e.g.} hematopoietic patients. The aim of this paper was to analyse the \textit{in vitro} activity of micafungin against 30 clinical isolates of non-\textit{albicans} Candida spp. (C. \textit{glabrata}, C. \textit{famata}, C. \textit{tropicalis}, C. \textit{inconspicua}, C. \textit{lusitaniae}, C. \textit{parapsilosis}, C. \textit{krusei}) by way of the E-test procedure, allowing determination of minimal inhibitory concentration (MIC). Data presented in this paper indicate that most of the studied clinical isolates – 27 (90\%) showed sensitivity to micafungin, with MIC values ranging from 0.004 to 2 mg/l, while 3 (10\%) isolates, including 2 isolates of \textit{C. tropicalis} and 1 isolate of \textit{C. famata}, were resistant to micafungin, with MIC values > 32 mg/l. The MIC\textsubscript{90} and MIC\textsubscript{50} values of micafungin, defined as MIC inhibited growth of 50\% or 90\% of the isolates studied, were 0.008 mg/l or 2 mg/l, respectively. In the case of \textit{C. glabrata} isolates, MICs ranged from 0.004 to 0.016 mg/l, while MIC\textsubscript{90} was 0.004 mg/l and MIC\textsubscript{50} 0.008 mg/l. Our data confirm the utility of micafungin for the therapy of the infections caused by non-\textit{albicans} Candida spp., especially \textit{C. glabrata}.

\textbf{INTRODUCTION}

Invasive fungal infections induced by \textit{Candida} spp. are a significant cause of morbidity and mortality worldwide. Moreover, changes in the spectrum of \textit{Candida} spp. responsible for candidiases have been observed in recent years. Currently, the major pathogen is still \textit{C. albicans} (more than 75\% of infections), while the incidence of non-\textit{albicans} \textit{Candida} spp. infections is steadily increasing. Indeed, the prevalence of \textit{C. glabrata} infections has increased from 2 to 26\%, that of \textit{C. tropicalis} – from 2 to 24\% and that of \textit{C. parapsilosis} – from 9 to 20\% \cite{2,13,14}, especially in patients from several risk groups. These groups of patients include those undergoing surgical procedures, those with intravenous drug administration, organ transplant recipients, oncology patients and individuals with some endocrinological disorders (\textit{e.g.} diabetes mellitus) \cite{2,13,14}.

Micafungin belongs to a unique class of new antifungals known as the ‘echinocandins’. Its antifungal mechanism is based on the inhibition of 1,3-β-D-glucan biosynthesis, an essential polysaccharide that is a main structural component of the fungal cell wall, which in turn, is responsible for structural cell integrity and osmotic stability \cite{1,4,7,10,12,35,36}. At the moment, micafungin is the first-line treatment for invasive and deep-seated \textit{Candida} spp. infections and has excellent antifungal effects \textit{in vitro} against the yeast strains resistant to amphotericin B and azoles, especially to \textit{C. glabrata} (which is intrinsically resistant to fluconazole) \cite{6,16,18,20}. Micafungin is also recommended in treating candidiasis ranging from superficial infections, such as oral thrush and vaginitis, to systemic and potentially life-threatening diseases, \textit{e.g.} esophageal candidiasis or candidemia \cite{8,9,15,19,21}. However, there is a need to monitor the sensitivity of \textit{Candida} spp. clinical isolates to echinocandins, including micafungin, in order to assess the rate of resistance to these drugs. The aim of this paper was to analyse the \textit{in vitro} activity of micafungin by the E-test procedure, against 30 clinical isolates of non-\textit{albicans} \textit{Candida} spp. derived from different clinical specimens obtained from hospitalized patients, especially hematopoietical persons.

\textbf{MATERIAL AND METHODS}

The study protocol (No. KE-0254/75/2011) was approved by the Ethical Committee of the Medical University of Lublin. In it, clinical specimens (\textit{e.g.} blood, spit, urine,
The activity of micafungin against clinical isolates of non-albicans Candida spp.

Pharmacists and medical scientists are faced with the challenge of increasing frequency of fungal infections due to the rise of antifungal resistance. Micafungin is an echinocandin used as an antifungal agent that inhibits the growth of fungi. This study aimed to assess the susceptibility of non-albicans Candida spp. clinical isolates to micafungin through the E-test method.

**RESULTS**

As shown in Table 2, most of the studied clinical isolates of non-albicans Candida spp. (27/30, 90%) showed sensitivity to micafungin, with MIC values ranging from 0.004 to 2 mg/l, while 3 (10%) isolates, including 2 isolates of C. tropicalis and 1 isolate of C. famata were resistant to micafungin – with MIC values > 32 mg/l. The isolates were identified by biochemical and microtost API 20 C AUX (bioMerieux), on the basis of assimilation of various substrates.

**DISCUSSION**

The increased frequency of fungal infections in recent years is associated with several factors, including inappropriate use of antifungal drugs. Our data indicate that most of the studied clinical isolates of non-albicans Candida spp. (C. glabrata, C. famata, C. tropicalis, C. inconspicua, C. lusitaniae, C. parapsilosis, C. krusei) obtained from hospitalized patients showed sensitivity to micafungin, with a MIC range of 0.004 to 2 mg/l. These data are in accord with the results presented by other authors, wherein micafungin showed good activity in vitro against a broad range of Candida spp. As reported by Nguyen et al. [23], MIC of micafungin ranged from 0.008 to 0.125 mg/l for C. glabrata and C. krusei, and from 0.5 to 1 mg/l for C. parapsilosis. Pfaller et al. [26] found that micafungin was very active against non-albicans Candida spp. (C. glabrata, C. tropicalis, C. kefyr, C. krusei, C. lusitaniae, C. guilliermondii, C. parapsilosis) isolated from different clinical specimens from patients in 100 medical centers, in the years 2003 – 2007, with MIC ranging from 0.015 to 1 mg/l. Similar data were reported by other authors [11,17,22,25,32,33], who reveal that micafungin was active against clinical isolates of C. tropicalis, C. glabrata, C. parapsilosis, C. dubliniensis and C. krusei.
C. krusei, with a MIC range from 0.002 to 1 mg/l. Of note, higher MIC values of micafungin (≥ 2 mg/l) were usually evidenced for C. tropicalis and C. parapsilosis [17,32,33].

There has been a gradual increase in the incidence of C. glabrata related nosocomial infections. The treating of these infections can be difficult because this species may be resistant to fluconazole. Micafungin, a newer antifungal agent, provides an alternative and effective therapy against C. glabrata infections, especially that caused by the isolates which had developed resistance to fluconazole [6,20]. Indeed, C. glabrata is naturally about 8-fold more insensitive to fluconazole than C. albicans. A study performed in the US showed the very high efficiency of micafungin in treating C. glabrata infections caused by the isolates resistant to fluconazole, and which were obtained from patients with candidiases of the oral cavity and throat [20]. The data presented in this paper showed that clinical isolates of C. glabrata were highly susceptible to micafungin, with MIC ranging from 0.004 to 0.016 mg/l.

Echinocandins are a relatively new group of antifungals, and, currently, resistance to them is rare [30,31,38]. Our data indicate that only 10% of clinical isolates of non-albicans Candida spp. (C. tropicalis, C. famata) were resistant to micafungin, with MIC ≥ 32 mg/l. It should be noted that breakpoint for micafungin-resistant strains is > 2 mg/l [3]. As found by Pfaller et al. [27,28,29], MIC of micafungin for only a few clinical strains of non-albicans Candida spp., e.g. C. tropicalis and C. parapsilosis were higher than 2 mg/l, indicating insensitivity of the isolates. What is more, other authors found that some isolates of C. glabrata, C. tropicalis and C. parapsilosis obtained from different clinical materials in patients suffering from candidiases, showed MIC above 2 mg/l, this figure deciding about their resistance to this agent.

The MIC₉₀ and MIC₉₀ of micafungin for non-albicans Candida spp. isolates, obtained in the present study were 0.008 mg/l and 2 mg/l, respectively. Similar data were reported by Pfaffer et al. [27-29]. These authors revealed that MIC₉₀ and MIC₉₀ of micafungin for Candida spp. (C. albicans, C. glabrata, C. tropicalis, C. parapsilosis, C. krusei and C. guilliermondii) isolated from different clinical centers in 2001-2006, were 0.015 – 1 mg/l and 0.015 – 2 mg/l, respectively. Furthermore, according to other authors [11,20], MIC₉₀ of micafungin for non-albicans Candida spp. (C. glabrata, C. tropicalis, C. parapsilosis, C. krusei, C. lusitaniae and C. guilliermondii) ranged from 0.015 to 0.5 mg/l, while MIC₉₀ ranged from 0.015 to 1 mg/l.

As reported in this paper, the MIC₉₀ of micafungin for C. glabrata isolates was 0.004 mg/l and MIC₉₀ = 0.008 mg/l. According to the data obtained by Pfaffer et al. [27,28,29], MIC₉₀ and MIC₉₀ of micafungin were 0.015 mg/l for C. glabrata isolates from different clinical materials obtained from several medical centers.

The presented data, showing the high in vitro activity of micafungin against non-albicans Candida spp. clinical isolates (including C. glabrata), along-side those from literature [5,24,34,37] concerning the in vitro data, as well as data derived from clinical trials, point to the clinical significance of micafungin as an alternative option in the therapy of candidiases, especially invasive ones.

CONCLUSION

The data presented in this paper demonstrate that most of the studied clinical isolates of non-albicans Candida spp. showed sensitivity in vitro to micafungin. These data confirm the utility of micafungin for the therapy of the infections caused by non-albicans Candida spp., especially C. glabrata.

REFERENCES

The activity of micafungin against clinical isolates of non-albicans Candida spp.