Development of New Strategies for Echinocandins: Progress in Translational Research

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Echinocandins are N-acyl–substituted cyclic hexapeptides with potent in vitro and in vivo activity against Candida species that are used for primary treatment and prevention of candidemia and invasive candidiasis. Recent progress in the translational research of echinocandins has led to new approaches for treatment of central venous catheter Candida biofilms. Other studies have laid the experimental and clinical foundation for use of extended dosing intervals for administration of echinocandins in treatment and prevention of candidemia and invasive candidiasis.

Keywords. echinocandins; anidulafungin; caspofungin; micafungin.

Echinocandins are N-acyl–substituted cyclic hexapeptides with potent in vitro and in vivo activity against Candida species [1–4]. These antifungal agents have emerged as primary therapy for candidemia and other forms of invasive candidiasis. The echinocandins also have been effective in prevention of candidemia in patients who are neutropenic for treatment of hematological malignancies or in the preparative regimens for hematopoietic stem cell transplant (HSCT). Aguilar-Zapata et al in this monograph review these indications, as well as other uses of echinocandins in treatment and prevention of invasive candidiasis [5].

In association with the expanded use of echinocandins, resistance to these compounds is increasingly reported. In this monograph, Perlin reviews mechanisms of resistance to echinocandins with thoughtful insights into the molecular basis for this emerging problem [6]. Although emergence of resistance to echinocandins during therapy remains infrequent, recognition of this problem in individual patients and centers is important.

The formation of Candida biofilms on vascular catheters provides a rational basis for their removal in patients with candidemia [7]. Among the challenges of management of candidemia are Candida biofilms produced on central venous catheters (CVCs) that warrant removal in many patients who already have limited vascular access [8]. Retention of CVCs by successful treatment of Candida biofilm in such patients would reduce costs and discomfort, as well as the risks of general anesthesia. Among patients with thrombocytopenia or coagulopathy, salvage of an infected CVC would also eliminate the risk for hemorrhage associated with surgical replacement.

Studies presented in this monograph of micafungin in the treatment of Candida biofilms establish an experimental rationale for retention of CVCs in the management of candidemia. Ghannoum et al review the data for the differential in vitro effects of antifungal agents in eradication of Candida biofilms [9]. These studies consistently demonstrate the efficacy of echinocandins in treatment of both the planktonic and biofilm populations of Candida species. Recent studies in animal models of CVC-related Candida biofilm further demonstrate successful treatment with the administration
of micafungin as lock solution and systemic therapy [10]. These studies provide a rational basis for development of a clinical trial for treatment of patients with candidemia in whom the CVC cannot be safely replaced. Such patients would include those with CVC-related candidemia whose management is restricted by limited venous access or thrombocytopenia.

As an extension of our understanding of CVC infections is the challenge of treatment of Candida biofilms on other surfaces, particularly that of mucosal epithelium and vascular endothelium. Katragkou and colleagues review the pathogenesis and treatment of oropharyngeal candidiasis, vaginal candidiasis, and Candida endocarditis [11].

CVCs and other devices may be coinfected by Candida species and bacteria. Arvanitis and Mylonakis in this monograph describe these interactions in vivo using the murine models or the invertebrate systems of Caenorhabditis elegans and Galleria mellonella [12]. Based on their effect against fungal biofilms and their immunomodulatory properties, echinocandins have the potential to be useful in polymicrobial infections and in high-risk complex infections such as ventilator-associated pneumonia or sepsis where involvement by fungi may lead to worsened outcomes.

Yet another challenge in treatment and prevention of candidemia and other forms of invasive candidiasis is the need for daily intravenous administration of echinocandins. Administration of an echinocandin over a longer dosing interval would allow ambulatory care, improve quality of life, reduce costs of intravenous administration, and lower the frequency of accessing of CVCs. In this supplement, Gumbo reviews the pharmacokinetic and pharmacodynamic rationale for novel regimens of micafungin with extended dosing intervals in treatment of experimental disseminated candidiasis [13]. As further demonstration of this important concept, Petraitiené and colleagues report the pharmacokinetics and efficacy of micafungin in treatment of disseminated candidiasis in persistently neutropenic hosts with eradication of infection in multiple tissue sites [14]. These experimental data [13, 14] collectively provide the laboratory foundation for clinical trials examining strategies for extended dosing intervals from every 3 days to as long as once weekly for treatment or prevention of disseminated candidiasis.

The use of extended dosing intervals of a given echinocandin requires higher single doses than those that are routinely administered for daily dosing. Several studies support the safety of higher doses of micafungin in pediatric and adult patients over a wide dosage range [15–21].

The study by Neofytos and colleagues exemplifies this dosing strategy in reporting a single-center observational study of the safety and efficacy of intermittent administration of high-dose micafungin of ≥5 doses of 300 mg of micafungin given 2 and/or 3 times weekly in a 5-year cohort of 104 allogeneic HSCT recipients [22]. Serum aspartate aminotransferase, alanine aminotransferase, and alkaline phosphatase levels decreased from baseline to end of treatment (P < .001). Patients with normal baseline liver function maintained similar enzyme levels throughout the study. For those patients with abnormal baseline serum hepatic enzymes, there was a significant improvement from baseline to end of treatment (P ≤ .005).

Higher dosages of echinocandins carry important implications for cardiac toxicity. Recent studies by Cleary and associates have elucidated a differential cardiotoxic effect of echinocandins [23, 24]. The article by Cleary and Stover in this monograph discusses the progress in understanding this drug-induced cardiomyopathy [25]. They report that echinocandin-related cardiac dysfunction is a mitochondrial drug-induced disease caused by focal direct myocyte injury. The data indicate that whereas caspofungin or anidulafungin administration into the heart via central line induced significant decline in contractility, micafungin was not associated with altered cardiac function in this system. Differences in lipophilicity of the echinocandins may account for these properties’ acute cardiotoxicity.

The paradoxical effect on growth and morphology in Candida species and Aspergillus species is another consequence of high concentrations of echinocandins [26–31]. The paradoxical effect of echinocandins on Candida species and Aspergillus species is growth that occurs at high echinocandin concentrations above the minimum inhibitory concentration. Paradoxical growth varies in terms of media, species, strain, and type of echinocandin. The in vivo and clinical significance of the paradoxical effect is uncertain. Steinbach et al discuss the mechanisms of the paradoxical effect of echinocandins on Aspergillus species with calcineurin and Hsp90 cell signaling pathways regulating the observed cellular and structural changes [32].

Finally, as new uses and strategies are developed for echinocandins, one must address the regulatory pathways needed for bringing innovative translational research to patient care. Tillotson and Tillotson in this monograph discuss the current unmet clinical needs, the challenges to conducting clinical trials, and the current US regulatory positions for developing new compounds and strategies [33].

We therefore hope that this monograph and the translational research summarized herein will provide a timely, succinct, and useful resource for understanding the expanding role echinocandins in antifungal therapeutics.

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References