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SUPPLEMENT ARTICLE

Pharmacology of Liposomal Amphotericin B: An Introduction to Preclinical and Clinical Advances for Treatment of Life-threatening Invasive Fungal Infections

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Amphotericin B (AmB) is characterized by a broad spectrum of antifungal efficacy and is an essential compound in the antifungal armamentarium. However, the clinical utility of AmB has been restricted by dose-limiting and potentially fatal nephrotoxicity. During the past 4 decades, major advances have been achieved in the development of lipid formulations of AmB, with the key objective of attenuating its nephrotoxicity. Liposomal amphotericin B (LAmB; AmBisome) has emerged as the most widely used agent of the licensed lipid formulations of AmB for the treatment of invasive fungal infections [1–3]. For the purpose of this article, the term "LAmB" refers exclusively to AmBisome.

During a recent meeting of the authors, organized by Gilead to discuss the recent advances and unmet needs in the use of LAmB, a decision was made by the authors to provide a definitive review of this important compound. Written by distinguished experts in antifungal drug development, medicinal chemistry, pharmacology, medical mycology, immunopharmacology, infectious diseases, and hematology/oncology, this supplement consists of 2 important articles on the preclinical and clinical safety, tolerability, pharmacokinetics (PK), pharmacodynamics, and efficacy of LAmB [4, 5]. The two articles (Adler-Moore et al [4] and Groll et al [5]) presented in this supplement of *Clinical Infectious Diseases* provide an unprecedented, comprehensive body of knowledge on the mechanisms of action, toxicology, pharmacology, and efficacy of this important antifungal agent.

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PRECLINICAL PHARMACOLOGY AND THERAPEUTICS

The first article by Adler-Moore et al on preclinical pharmacology and therapeutics begins with a review of the mechanisms of antifungal activity of AmB [4]. The review discusses AmB's interaction with ergosterol in the fungal cell membrane to form subunit oligomers of membrane-permeabilizing ion channels that promote leakage of intracellular K+ and Mg++ ions with a reciprocal influx of Na+ and Ca++ ions, resulting in a potentially lethal effect on fungal cellular viability [6–8], as well as other mechanisms of action. The authors then provide an in-depth review of recent data exploring how the binding affinity of liposomes for fungal cell walls contributes to the capacity of LAmB to traverse the cell wall and bind with cell membrane ergosterol in the targeted fungus [9, 10].

TOXICOLOGY

Adler-Moore et al then discuss how the reduction in drug-induced nephrotoxicity through the use of LAmB has been an important advance in antifungal therapy [11]. LAmB attenuates nephrotoxicity due to the presence of cholesterol within the liposome bilayer that binds to AmB, thus permitting AmB to remain associated within the liposome rather than interacting with renal tubular epithelial cells [12]. The authors continue with a review of the results in predictive animal models that have demonstrated this reduced nephrotoxicity compared with that of deoxycholate amphotericin B (DAmB) [13–15], as well as randomized clinical trials that have since demonstrated significant reductions in nephrotoxicity, particularly glomerular injury with LAmB compared with DAmB [16–18]. The authors discuss the mechanisms of infusion-related toxicity (IRT) associated with LAmB, the frequency and severity of which are also considerably reduced compared with IRT associated with DAmB [16]. The authors also elaborate on a distinctive severe acute infusion-related reaction associated with LAmB and classified as a unique type 1 hypersensitivity reaction termed "complement activation-related pseudoallergy" [19].

Adler-Moore et al continue with a review of the preclinical studies of LAmB in the treatment of different fungal infections including pulmonary aspergillosis [13], cryptococcal meningitis [20], central nervous system aspergillosis [21], *Candida* meningoencephalitis [22], mucormycosis [23, 24], and coccidioidal meningitis [25]. The authors discuss the pharmacodynamic effects of DAmB and LAmB in several different animal model systems as being principally determined by the C_{max}/minimum inhibitory concentration ratio [26–28].

CLINICAL PHARMACOLOGY AND THERAPEUTICS

In the second article, Groll et al [5] initially review the PK studies of LAmB in healthy adult volunteers, as well as adult and pediatric patients [29–33]. The authors then review the clinical studies of the efficacy of LAmB against candidiasis [34–37], aspergillosis [38], cryptococcosis [39, 40], histoplasmosis [18], mucormycosis [41, 42], and other less common, deeply invasive mycoses, such as fusariosis [43]. The review delineates the role of LAmB in early treatment and preventive strategies of empirical antifungal therapy [17, 44] and prophylaxis [45, 46] in high-risk patient populations.

When considering future directions, both articles underscore the need for new dosing strategies of LAmB for the treatment and prevention of invasive fungal infections that are based on predictive preclinical and sound clinical PK data for invasive mycoses, particularly infections with emerging triazole-resistant pathogens.

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Disclaimer. The views, opinions, assumptions, or any other information set out in this article are solely those of the authors and should not be attributed to the funders or any person connected with the funders. Liposomal amphotericin B is not approved for prophylaxis.

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