Aerosolization of Liposomal Amphotericin B (AmBisome®) Maintains Antifungal Drug Concentrations in Lungs for up to Five Days Post-Treatment

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ABSTRACT

In immunocompromised patients, infection by Aspergillus species has life threatening effects. It causes severe pneumonia and results in patient mortality in at least 50% of treated patients and 30-60% of untreated patients (Shaunak et al., 2015). The immunocompromised population susceptible to infection by Aspergillus species is comprised of a wide array of patients such as those suffering from bone marrow and organ transplants as well as patients receiving treatment for certain cancers, severe burns, and AIDS. Fungal infections such as aspergillosis can kill patients who have otherwise been successfully treated for the condition that resulted in their initial hospitalization. The extensive complications caused by invasive aspergillosis and the high mortality associated with this infection makes the study of its treatment very important.

AmBisome, the lipid formulation of Amphotericin B, is one of the first-line therapies for treating invasive aspergillosis (Paterson et al., 2000). AmBisome is significantly less toxic and better tolerated than other forms of amphotericin B therapy. Several studies have shown the prophylactic use of aerosolized AmBisome therapy in preventing invasive pulmonary aspergillosis and in clinical trials, patients experienced no serious adverse events due to the inhalation of AmBisome (Rijnsoever et al., 2015). It is possible that aerosol treatment could be more effective for treating pulmonary fungal infections as it allows for the drug to concentrate in the lungs which is the place where most infections occur (Schiller et al., 2015).

In order to study the potential for aerosol therapy in treating pulmonary aspergillosis in people, an animal model has to be used as a critical step in evaluating different dosing regimes and different doses of the drug to maximize the feasibility of this approach. To investigate this we standardized an aerosol delivery system for AmBisome (liposomal amphotericin B) in mice, and compared how much drug was delivered to the lungs, liver, kidneys and spleen following different numbers of treatments.

RESULTS

The aerosol delivery method achieved amphotericin B drug concentrations at least 4x the MIC (2 - 4 µg/g) for Aspergillus species (17.67 µg/g with three treatments).

With three treatments, amphotericin B was retained in the lungs for 24h, 72h, and 120h at concentrations of 17.67, 14.01, and 11.13 µg/g of tissue. The amphotericin B remained in the lungs well above the MIC for at least 5 days.

AmBisome was found in the spleens for all treatment groups only at 120h, suggesting delayed splenic uptake following aerosol administration.

The aerosol apparatus delivered AmBisome at low concentrations to liver and kidney, which is advantageous since intravenous AmBi exhibits limited hepatotoxicity and nephrotoxicity.

CONCLUSIONS

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Future Studies

Determine the concentration of aerosolized AmBisome in immunosuppressed mice administered once every 24h, for three consecutive twenty-minute treatments.

Investigate the efficacy, pharmacodynamics, and pharmacokinetics of aerosolized AmBisome alone or in combination with follow-up intravenous AmBisome for the treatment of pulmonary aspergillosis in Swiss-Webster mice.

REFERENCES