A Novel Encocchleated Atovaquone Formulation is Active in a Murine Model of Pneumocystis Pneumonia

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Background

- Pneumocystis spp. are yeast-like fungi that can cause Pneumocystis pneumonia (PCP) in immune-compromised hosts. Over the past two decades, the incidence of PCP in HIV-infected individuals in the United States has declined, mostly due to the widespread use of prophylaxis in patients whose CD4 counts are acceptable, as well as the development of Highly Active Anti-Retroviral Therapy (HAART). However, for those who develop PCP, the associated mortality in the United States remains relatively stable at 10%.
- Trithropem/sulfamethoxazole (TMX-SMX) is the standard of care treatment for pneumocystis pneumonia (PCP); however, it requires a high rate of adverse events (20-85% including rash, fever, neutropenia, and bone marrow suppression).
- Subsequently, up to 30% of patients experience toxicity that leads to discontinuation of TMX-SMX.
- Atovaquone is an alternative agent for the treatment and prophylaxis of PCP in immunocompromised patients who are unable to tolerate trithropsulfamethoxazole.
- The current commercially available formulations of atovaquone suffer from limitations of salable pharmacokinetics and poor tolerance due to complaints of poor taste/palatability, nausea, diarrhea, rash, headache, and transaminase elevations, with up to 20% of patients discontinuing treatment due to adverse events.
- Cochleates are stable, orally bioavailable, lipid nanoparticles that can improve intestinal absorption and mitigate taste and palatability issues.
- In a previous study of a different formulation of CATQ, promising efficacy was observed, however, a toxicity of papillary necrosis developed in mice treated with CATQ plus anidulafungin.
- We sought to evaluate the PK, efficacy, and toxicity of a novel a novel lipid crystal nanoparticle formulation of encocchleated atovaquone (CATQ) in a murine model of pneumocystis pneumonia.

Study Design and Methods

Murine infection model:
- Mice immunosuppressed with dexamethasone and infected with P. murina infected by cohousing with a P. murina infected mouse and the drinking water to 5% were used in all three studies.

Efficacy study 1:
- Infected mice (N = 8) were treated daily for 14 or 21 days with different atovaquone formulations.
- The 100 mg/kg dose of CATQ was statistically significant improvement in survival versus the C/S group at day 14. There was no difference noted in the lung between groups in regard to organism involvement: The combination of anidulafungin with either the encochleated or the empty cochleates has significantly reduced burdens, suggesting this combination had increased efficacy after 14 days of treatment. All treatment groups had reduced inflammation when compared to the untreated mice, likely due to the decreased organism burdens and Decreased Beta-glucan levels in the anidulafungin groups. The only group to have reduced consolidation was the anidulafungin + empty cochleates.

PK Study:
- CATQ demonstrated a favorable PK distribution profile, with a half-life ~13 hours in plasma and ~50 hours in interstitial water levels in both plasma and lung through 96 hrs post-dose.

Disclosures & Funding

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Conclusion

CATQ represents a viable potential therapeutic candidate for treatment and prophylaxis of PCP with further development warranted.