Introduction

Nontuberculous mycobacteria (NTM) infection is a growing health threat to both non-CF and CF patients. These infections have been shown to reduce lung function and survival. Despite this, there remains limited treatment options for NTM-PD that are both safe and effective. Treatment strategies involve long, intensive, systemic antibiotic regimens, often involving toxicity/adverse drug reactions. Ongoing studies are evaluating QRM-003 (Clofazimine inhalation suspension) to effectively reduce bacterial burden in NTM-infected mouse models of both Mycobacterium avium and Mycobacterium abscessus.

Hypothesis

1) QRM-003 will lead to greater pulmonary accumulation than oral clofazimine.
2) QRM-003 delivery will reduce clofazimine accumulation in extrapulmonary tissues.

Study 1: Clofazimine Distribution in Naïve Mouse Models

- Naïve C57Bl/6 mice were administered either oral clofazimine (20 mg/kg) or QRM-003 (28 mg/kg) daily for 10 days.
- On Day 10, lung, spleen, and liver tissues were collected to quantify clofazimine accumulation.

Study 2: Clofazimine Distribution in Chronic NTM Infection Models

- In the chronic infection model, there was no significant difference in plasma concentrations between oral delivery and QRM-003. QRM-003 administration led to significant increases in pulmonary tissue concentrations compared to oral clofazimine administration, even after accounting for differences in dose. QRM-003 did not lead to significant differences in extrapulmonary tissue concentrations, despite administration of higher doses, after 10 days treatment.

Conclusions

- Oral clofazimine administration has often been associated with a number of adverse events, such as skin discoloration, ichthyosis and gastrointestinal intolerance, which may be due to its extrapulmonary tissue accumulation.

Purpose: To compare the tissue accumulation of clofazimine following oral and inhaled drug delivery.

Data to date suggests QRM-003 treatment can lead to increased lung tissue accumulation, and a reduction in extrapulmonary tissue concentrations. This should lead to a reduction in off-tissue side effects, while improving antimicrobial clearance from pulmonary tissue.

Ongoing studies are evaluating QRM-003 pharmacokinetics in both pulmonary and extrapulmonary space.

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References