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Inhaled, Nebulized Clofazimine for the Treatment of Pulmonary Nontuberculous Mycobacteria Disease Offers the Prospect of Convenient Dosing and Prolonged Activity

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Abstract

Orally or intravenously administered antibiotics have been successfully reformulated for delivery via inhalation and treatment of serious, chronic lung infections. Oral clofazimine has shown microbiological efficacy in patients with pulmonary nontuberculous mycobacterial (NTM) disease, a condition that is increasingly prevalent and associated with substantial morbidity. However, systemic administration of clofazimine can lead to drug accumulation in extrapulmonary tissues and clinically significant adverse reactions in non-target organs such as gastrointestinal side effects, QT prolongation, and skin discoloration. To overcome these limitations, an inhaled formulation of clofazimine has been developed and tested preclinically and in healthy human volunteers. Preliminary evidence suggests that inhalation of clofazimine can achieve drug concentrations in lung tissue greater than the minimal inhibitory concentration (MIC) for prolonged periods and relatively low drug concentrations in plasma, potentially broadening the therapeutic index. In this article, we review the available data for inhaled clofazimine and highlight its potential as a treatment for pulmonary NTM disease.

Keywords: Clofazimine; Nebulization; Nontuberculous mycobacteria; Inhaled antibiotics; Lung targeting; Intermittent dosing

Abbreviations AUC0-24h: Area under The Concentration-Time Curve from 0 to 24 hours; CF: Cystic Fibrosis; Cmax: Maximum Concentration; MABSC: M. abscessus Complex; MAC: M. avium Complex; MIC: Minimum Inhibitory Concentration

Introduction

Substantial advances have been made in the field of inhaled antibiotics, particularly in Cystic Fibrosis (CF) and non-CF bronchiectasis [1]. In patients with respiratory infections related to these conditions, pulmonary administration of antibiotics can achieve drug concentrations in lung tissue that are sufficiently high to reduce the bacterial load and ameliorate associated clinical manifestations. Furthermore, topical delivery of antibiotics directly to the site of infection minimizes drug levels in circulation and thereby can avoid off-target adverse events as well as drug interactions with systemically administered medications. For example, inhaled aztreonam (Cayston®), which is approved and commonly used for the treatment of P. aeruginosa infection in patients with CF, exhibits a favorable risk-benefit balance compared to systemic administration of aztreonam alone [2]. Pulmonary Nontuberculous Mycobacteria (NTM) disease represents another serious, chronic condition that might be amenable to treatment with inhaled antibiotics. The development of inhaled clofazimine as a therapy for pulmonary NTM disease aims to apply the advantages of local antibiotic delivery with the ultimate goal of addressing an emerging public health threat.

Literature Review

Approximately 90,000 people are living with pulmonary NTM disease in the USA and the prevalence of the condition is increasing, according to the American Lung Association [3]. Pulmonary NTM infections are most commonly caused by the *M. avium* Complex (MAC) and *M. abscessus* Complex (MABSC). Signs and symptoms of NTM pulmonary infection include chronic cough, fatigue, weight loss, fever, and night sweats. Treatment often requires the use of a three-drug regimen of orally administered antibiotics that are taken continuously for years and are known to result in clinically significant adverse reactions and suboptimal outcomes [4]. The first inhaled treatment option for pulmonary NTM disease, amikacin (Arikayce®), received accelerated approval for a limited population of adult patients with MAC infection resistant to treatment with a regimen of multiple oral antibiotics [5]. While the introduction of inhaled amikacin is a notable advance, its continued approval may be contingent upon demonstration of clinical benefit in ongoing confirmatory trials and, perhaps more importantly, respiratory adverse reactions including cough and bronchospasm have been commonly observed with the use of inhaled amikacin.

Previous successes in the field of inhaled antibiotics typically have involved the “repurposing” of older drugs that had been available only for oral or intravenous delivery prior to the development of an inhaled formulation. Similarly, clofazimine is an oral antimycobacterial agent that was approved in the USA for the treatment of lepromatous leprosy in 1986 but is no longer marketed. For pulmonary NTM

infections, oral clofazimine has shown effectiveness as demonstrated by bacterial culture conversion [6,7]. However, the oral route of administration and consequent high concentrations of clofazimine in plasma can lead to drug accumulation in extrapulmonary tissues and systemic toxicities including gastrointestinal side effects, QT prolongation, and skin discoloration and other skin reactions [8]. Given the efficacy and safety profile of oral clofazimine in pulmonary NTM disease, it was identified as a promising candidate for a drug repurposing project, ie, development of inhaled clofazimine with the objectives of maintaining or improving antimycobacterial activity while reducing or eliminating systemic toxicities. The potential for a favorable safety and efficacy profile of the inhaled formulation warrants continued investigation of pulmonary delivery of clofazimine to improve treatment outcomes in this currently underserved patient population.

Initially, the antimycobacterial activity of clofazimine was demonstrated against MAC and MABSC infections in both *in vitro* and *in vivo* models [9]. In *in vitro* studies, Minimal Inhibitory Concentrations (MICs) of clofazimine against several strains of MAC and MABSC ranged from 0.125 to 2 μg/mL. In particular, clofazimine was tested and showed *in vitro* activity against macrolide- and amikacin-resistant MAC, amikacin-resistant MABSC, and other macrolide-resistant mycobacterial species and strains. As macrolides are the mainstay of treatment for NTM infections and amikacin the treatment of last resort for macrolide-resistant NTM infections, these data are important and could support the use of inhaled clofazimine for the treatment of both drug-susceptible and drug-resistant mycobacterial lung disease. Statistically significant reductions in bacterial recovery from lung, liver, and spleen tissue were reported in mouse models of both acute and chronic MAC and MABSC infection following repeated administration of clofazimine by intratracheal instillation. The potent activity of clofazimine documented in these preclinical models was encouraging and supported further investigations in animals and humans.

Kunkel, et al., recently evaluated the toxicokinetics of inhaled clofazimine in dogs [10]. In this study, low, medium, and high doses of inhaled clofazimine as determined from prior studies in mice and rats were administered via a nebulizer once daily for 28 days. Clofazimine concentrations in the lung exceeded the average NTM MIC for all dose levels at all timepoints, including at 28 and 56 days after the last dose had been administered. However, plasma levels of clofazimine were consistently measurable only through 14 days post dosing. These data document the ability of an inhaled formulation of clofazimine to load the drug in lung tissue and avoid high levels in plasma. Concordant with these toxicokinetic findings, systemic adverse events of interest due to the safety profile of oral clofazimine were not observed; specifically, no skin discoloration or electrocardiogram abnormalities were observed. Another auspicious finding in this canine study was the persistence of "above MIC" target drug levels in the lung for at least two months following the cessation of dosing. Based on these data, a planned Phase 2/3 clinical trial in patients with pulmonary NTM disease will evaluate repeated cycles of one-month-on, two-months-off dosing of inhaled clofazimine. It is believed this intermittent regimen will be convenient for patients, will increase their acceptance of and adherence to inhaled clofazimine therapy, and will reduce their overall burden of treatment. Regular drug holidays also will limit the frequency with which patients must handle inhaled clofazimine, which has a red-orange color and could be bothersome to wash off the hands or clothes.

Discussion

A Phase 1, single-ascending-dose and multiple-ascending-dose study in Australia (Australian New Zealand Clinical Trials Registry number ACTRN12621001702808 was conducted to investigate the safety and pharmacokinetics of inhaled clofazimine in healthy volunteers. Initially, 24 subjects each received a single dose of 30 mg, 60 mg or 90 mg clofazimine or placebo administered via a PARI eFlow nebulizer; these doses were equivalent to lung-deposited doses of 10 mg, 20 mg, or 30 mg, respectively. Subsequently, an additional 16 subjects received once-daily doses for 7 days of 30 mg or 90 mg clofazimine or placebo. Inhaled clofazimine was safe and well tolerated. Adverse events predominantly were mild, with the few Grade ≥ 2 adverse events reported in the placebo group and/or considered by the investigator to be unrelated to study treatment. There were no adverse events resulting in treatment discontinuation, no serious adverse events, and no deaths. No adverse events of discoloration of the skin, hair, sputum, sclera, or tears; changes in visual acuity; QT prolongation; or changes in Columbia–Suicide Severity Rating Scale scores were reported. With regard to pharmacokinetics, increases in Cmax and AUC0-24 following administration of single and multiple doses were dose-proportional. The mean terminal half-life was 24 to 26 hours following a single dose but increased to 290 to 300 hours after once-daily doses for 7 days. Importantly, meaningful accumulation following multiple doses of inhaled clofazimine was observed; Cmax accumulation ratios were (Cmax on Day 7/ Cmax on Day 1) were 2.5 and 3.4 at 30 mg and 90 mg, respectively, and AUC0-24 accumulation ratios were (AUC0-24 on Day 7/ AUC0-24 on Day 1) were 2.8 and 3.9 at 30 mg and 90 mg, respectively. The observation of dose-dependent accumulation in the Phase 1 study supports the use of flexible dosing regimens consisting of relatively short dosing periods followed by longer drug holidays during which clofazimine remains present and active in the lung. Overall, these Phase 1 safety and pharmacokinetic data provide a basis for late-stage clinical development of inhaled clofazimine as a treatment for pulmonary NTM infections. Inhaled antibiotics have been associated with respiratory side effects [11]. As noted above, cough and bronchospasm are commonly reported in patients with pulmonary NTM disease receiving inhaled amikacin. In some cases, such adverse events lead to interruption of inhaled amikacin for up to 14 days or reduction in dosing frequency from every day to 3 days a week until resolution of symptoms. Additional warnings and precautions included in the prescribing information for inhaled amikacin include ototoxicity, nephrotoxicity, and neuromuscular blockade. The approved dose of inhaled amikacin, 590 mg, is considerably higher than the doses of inhaled clofazimine (30 to 90 mg in the Phase 1 study), reflecting the lower MIC and higher potency of clofazimine against NTM infections. Collectively, the preliminary evidence from the Phase 1 study suggests that inhaled clofazimine may be well tolerated in the lung and systemically. The rate of respiratory and other side effects will be monitored in the planned Phase 2/3 clinical trial.

Conclusion

In summary, past experience with various drug substances have demonstrated that inhaled antibiotics are beneficial as they reliably achieve higher drug concentrations in the lung compared to systemic administration and are safer as they avoid accumulation in non-target organs as well as interactions with orally or intravenously administered medications. Building on the progress to date in this

field, an inhaled formulation of clofazimine has been developed and tested preclinically and in healthy volunteers. The hypothesis of this development program is that inhaled clofazimine will prove advantageous relative to oral clofazimine, as it has been designed to safely improve the speed and magnitude of bacterial clearance by increasing local antibiotic concentrations in the lung and minimizing extrapulmonary exposure. The long lung residence time of clofazimine will allow for intermittent dosing, including off months, and thereby reduce the burden of treatment for patients. Potential downstream benefits to the patient include reductions in hospitalization and cost of illness. A forthcoming Phase 2/3 clinical trial of the efficacy and safety of inhaled clofazimine will be performed in patients who are already receiving guideline-based therapy with oral antibiotics but have not yet experienced conversion of cultured sputum samples from positive to negative for NTM infection. Other populations to be studied in the future may include newly diagnosed patients with pulmonary NTM disease and patients with fast- and slow-growing pulmonary NTM infections.

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