Novel administration of clofazimine for the treatment of Mycobacterium avium infection

Ethan Valinetz, MD; Helen Stankiewicz Karita, MD, MS; Paul S. Pottinger, MD; Rupali Jain, PharmD

1Department of Medicine, Division of Allergy & Infectious Diseases, University of Washington School of Medicine, 2Department of Pharmacy, University of Washington, Seattle, WA

Corresponding author: Ethan Valinetz, MD, University of Washington, Box 356423, 1959 NE Pacific Street, Seattle, Washington 98195, U.S., E-mail: edval89@gmail.com, Phone number: 206- 616-7217

Alternate corresponding author: Rupali Jain, PharmD, University of Washington, Box 356015, EA-152, Seattle, Washington 98195, U.S., E-mail: rupali@uw.edu, Phone number: 206-598-4416
Abstract

Clofazimine has demonstrated in vitro activity against many non-tuberculous mycobacteria. We present the case of a woman with cystic fibrosis who developed disseminated macrolide-resistant Mycobacterium avium infection following lung transplantation treated in part with clofazimine. We describe the novel administration of clofazimine via gastrostomy tube.

Keywords: clofazimine, gastrostomy tube, lung transplant, mycobacterium avium
Introduction

Clofazimine is a lipophilic r-iminophenazine antimicrobial originally studied for the treatment of tuberculosis that is currently FDA-approved for the treatment of *Mycobacterium leprae*.\(^1\) Clofazimine has demonstrated *in vitro* activity against other nontuberculous mycobacteria, including *Mycobacterium avium* complex (MAC).\(^2,3\) The off-label use of clofazimine has been described in patients with MAC infection, including patients living with HIV, cystic fibrosis, and requiring solid organ transplantation.\(^2,4-6\) It is currently available via Emergency Use Investigator-Initiated New drug application from Novartis. Clofazimine is supplied in the form of capsule for oral administration. According to the manufacturer, capsules should be swallowed whole and not opened or crushed.\(^1\) Due to the numerous adverse effects associated with prolonged administration of oral clofazimine (e.g., skin discoloration, depression, gastrointestinal intolerance), inhalational administration of clofazimine for pulmonary non-tuberculous mycobacteria treatment is currently under investigation.\(^7-10\) No recommendations are available for the administration of clofazimine in patients who are unable to take medications by mouth. We report the successful administration of clofazimine via gastrostomy tube to a post-lung transplant recipient with disseminated MAC infection.

Case Presentation

A 36-year-old woman with a history of cystic fibrosis and fibrocavitary pulmonary disease due to MAC underwent successful bilateral lung transplantation. Her MAC isolate was resistant to macrolides and amikacin. She had received ethambutol, rifampin, azithromycin, and clofazimine pre-transplant. The early post-operative course was complicated by severe hypoxia requiring transient extracorporeal membrane oxygenation support and ultimately required tracheostomy placement due to persistent respiratory failure. Her tenuous respiratory status precluded any
attempt to administer medications by mouth. During this period, she was continued on ethambutol via gastrostomy tube\textsuperscript{11} and intravenous azithromycin and rifampin. The clofazimine was held as there were no available guidelines for drug administration through a non-oral route. One-week post-transplant, blood and bronchoalveolar lavage (BAL) cultures were obtained for evaluation of fevers; MAC was isolated from both cultures after 4 weeks of incubation (Figure 1). Given disseminated MAC infection in the setting of her highly immunosuppressed state, we initiated off-label dosing of clofazimine via gastrostomy tube to optimize her MAC treatment regimen. In consultation with our investigational drug pharmacy team, a protocol for melted clofazimine administration via gastrostomy tube was developed (Figure 2). The clofazimine hard gelatin capsules were placed in a cup with 15 mL of hot water from an instant-hot water tap (approximately 120°F). A hemostat was used to macerate capsules into a small particle suspension. Through a syringe, the clofazimine suspension was administered via gastrostomy tube followed by water to decrease the risk of clogging. Enteral nutrition was held during medication administration and restarted afterwards. Because this administration method had not been previously evaluated, we initiated clofazimine at 300 mg daily instead of the 100 mg daily dose previously prescribed for treatment of her pulmonary MAC infection. To ensure drug absorption, clofazimine serum concentrations were measured by the National Jewish Health Mycobacteriology Laboratory. Five days after clofazimine initiation, serum concentrations were 0.5 mcg/mL at 2 hours post-administration (published reference range 0.5 to 2 mcg/mL\textsuperscript{12} and 0.47 mcg/mL after 6 hours. Drug levels were reported after 17 days of therapy on clofazimine; because these levels were within reference range before steady state had been reached, the clofazimine dose was decreased to the standard 100 mg daily. Repeat drug concentration levels obtained one day prior to reducing clofazimine dose were subsequently reported at 0.62 mcg/mL at 2 hours and 0.79 mcg/mL at 6 hours post-administration. A clofazimine trough level was obtained 54 days after decreasing the dose to 100 mg daily in order to verify that the patient was not reaching potentially toxic levels, and the trough concentration was 0.52 mcg/mL. In addition to clofazimine, azithromycin, rifabutin, and ethambutol, the patient was started on
bedaquiline and tedizolid. As the patient was on multiple QTc prolonging medications, weekly electrocardiograms were obtained and her QTc interval remained normal. Weekly hepatic function tests were normal while on the higher dose of clofazimine. The patient had already developed clofazimine-induced skin pigmentation prior to this hospitalization; skin discoloration remained stable despite higher doses of clofazimine. During her hospitalization, a new BAL culture obtained at 8 weeks post-transplant revealed persistent MAC pulmonary infection. Additionally, pleural fluid samples obtained at weeks 12 and 15 were acid fast bacilli smear positive, but culture negative. All subsequent blood cultures were negative for MAC. Ultimately, due to improved respiratory status, she was transitioned to oral clofazimine after 86 days of receiving this medication via gastrostomy tube. Despite several other complications during her prolonged hospitalization, her condition improved and she was discharged to a rehabilitation facility.

**Discussion**

In this report, we present our experience with a critically ill lung transplant recipient with disseminated MAC infection treated with clofazimine via gastrostomy tube. Non-tuberculous mycobacterial infections are a significant cause of morbidity and mortality, particularly in immunocompromised patients such as solid organ transplant recipients. Treatment regimens can be complex, and antimicrobials can be difficult to tolerate. Oral clofazimine has made a significant contribution to the treatment of MAC infections despite limited data supporting its use, but there is no official guidance for alternative route of administration for persons who cannot take medications by mouth.
Clofazimine is a highly lipophilic drug with extensive tissue distribution through accumulation in macrophages and adipose cells. Absorption after an oral administration of clofazimine is variable (45%-62%) and may be increased through concomitant food intake. Although the pharmacokinetics of clofazimine has only been partially elucidated, the reported half-life elimination of clofazimine is approximately 70 days and steady state concentration is achieved at 1 month. In the U.S., clofazimine is available via Investigational New Drug application to the FDA, with medication supplied by manufacturer Novartis. As indicated in the medication package insert, clofazimine is only approved for oral use. Although disintegration upon exposure to gastrointestinal fluid is a fundamental step for drug bioavailability of capsule formulations, it is unknown if changes in the physical property of clofazimine formulations can alter the drug pharmacokinetics.

In the present case, clofazimine was initiated via gastrostomy tube to augment the treatment regimen of her MAC infection. The optimal dose of oral clofazimine in immunosuppressed patients has not been established. In an observational study evaluating the use of oral clofazimine for pediatric and adults with pulmonary and extra-pulmonary nontuberculous mycobacterial infections as part of a multidrug regimen, most persons received clofazimine 100 mg daily. Dose adjusted treatment also included reduction of daily clofazimine to 50 mg and dose increased to 150 mg daily. In this immunosuppressed patient with mycobacteremia and unclear dose delivery and absorption, we opted to initiate clofazimine at a dose of 300mg daily (5.4 mg/kg/day). Although the dose was considerably higher than the recommended in the package insert, it was also unclear how much of the clofazimine would be delivered, absorbed, and whether the medication may adhere to the feeding tube itself. In a pharmacokinetics study conducted by van Ingen et al., 17 patients taking a mean daily clofazimine dose of 1.62 mg/kg were found to have a mean $C_{max}$ of 0.43 mcg/mL and mean final concentration of 0.44 mcg/mL. To optimize the clofazimine use while minimizing toxicity, we measured serum concentrations to ensure the clofazimine was absorbed prior to...
reducing the dose to 100mg daily (1.79 mg/kg/day). After 54 days of therapy, we measured a trough level to ensure that her serum concentration was not significantly elevated since she was closer to a steady state at that point. Although therapeutic drug monitoring can be used for dose adjustment for some antimicrobials, the role and clinical usefulness of therapeutic clofazimine drug monitoring is uncertain. However, in our patient, it provided reassuring information regarding systemic absorption.

There are multiple novel formulations of clofazimine currently under investigation.\textsuperscript{7-9,21-23} For instance, clofazimine can be processed to a dry powder for inhaled administration.\textsuperscript{8} Inhaled clofazimine reduced colony counts of \textit{Mycobacterium tuberculosis} in the lungs more significantly than oral clofazimine administration.\textsuperscript{9,10} Not surprisingly, inhaled clofazimine was inferior to systemic clofazimine at clearing non-tuberculous mycobacterial infections in the liver and spleen.\textsuperscript{10} Another clofazimine formulation can be prepared in a lipid-based solution via flash nanoprecipitation technology, although this formulation has not been tested \textit{in vivo}.\textsuperscript{21} Lastly, various groups have evaluated the possibility of parenteral administration of clofazimine. Peters et al. demonstrated reduced MAC burden in the liver, spleen, and lungs of the mice treated with intravenous clofazimine.\textsuperscript{23} Murashov et al. synthesized clofazimine hydrochloride microcrystals for parenteral administration and tested it in mice, showing that intravenous administration led to accumulation of clofazimine in macrophages.\textsuperscript{22} These studies are encouraging for the future use of alternative routes of clofazimine for the treatment of non-tuberculous mycobacterial infections.
In summary, this novel approach of melting clofazimine into a suspension for percutaneous gastrostomy tube administration should be considered for patients who are unable to take medications by mouth. Although therapeutic drug monitoring of clofazimine has not been established to improve clinical outcomes, drug levels could be helpful in persons with potentially altered gastrointestinal absorption. With this approach, we obtained therapeutic serum clofazimine levels and did observe clinical improvement in our patient, although this was likely multifactorial.
Acknowledgements

A special thanks to Janice Yamauchi, PharmD, Investigational Drug Services, and Charles Daley, MD, Chief of the Division of Mycobacterial & Respiratory Infections at National Jewish Health.

Conflict of Interest

None to disclose.

Funding

This work was supported by the University of Washington Host Defense Research Training Grant (T32AI007044, EDV), the Developmental Award from University of Washington Sexually Transmitted Infections Cooperative Research Center (U19AI11317, HCSK), and Research Supplement to Promote Diversity in Health-Related Research Program, National Cancer Institute at the National Institutes of Health (R01 CA213130-S, HCSK).
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Figure 1: Summary of clinical course

Figure 1 shows a summary of the patient’s clinical course with relevant microbiologic data and clofazimine start dates, dosing, and serum concentration levels.

Abbreviations: AFB, acid fast bacilli; BAL, bronchoalveolar lavage; MAC, Mycobacterium avium complex; mcg, micrograms; mL, milliliters; PEG, percutaneous endoscopic gastrostomy.
Figure 2 demonstrates the preparation (top panels) and administration (lower panels) of the clofazimine suspension. For preparation, fill dose cup with 15 mL hot water from instant hot water dispenser (120°F) and add clofazimine capsules. Macerate with hemostat to form a slurry. Draw up slurry for administration. Put on gloves prior to administration to prevent staining. Flush feeding tube with water prior to administration. Administer the clofazimine slurry and flush with water after administration to prevent clogging. Resume enteral nutrition afterwards. Do not administer with other medications. Administration may stain the feeding tube.

Abbreviations: F, Fahrenheit; mL, milliliters.