Open Forum Infectious Diseases

BRIEF REPORT

Novel Administration of Clofazimine for the Treatment of *Mycobacterium avium* Infection

Ethan Valinetz,[1] Helen Stankiewicz Karita,[1] Paul S. Pottinger,[1] and Rupali Jain[1,2]

[1]Division of Allergy & Infectious Diseases, Department of Medicine, University of Washington School of Medicine, Seattle, Washington, USA, and [2]Department of Pharmacy, University of Washington, Seattle, Washington, USA

Clofazimine has demonstrated in vitro activity against many nontuberculous 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*.

Clofazimine is a lipophilic r-iminophenazine antimicrobial originally studied for the treatment of tuberculosis that is currently Food and Drug Administration (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 with HIV, cystic fibrosis, and those requiring solid organ transplantation [2, 4–6]. It is currently available via the Emergency Use Investigator-Initiated New Drug Application from Novartis. Clofazimine is supplied in capsule form 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 (eg, skin discoloration, depression, gastrointestinal intolerance), inhalational administration of clofazimine for pulmonary nontuberculous 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 pretransplant. The early postoperative 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 [11] and intravenous azithromycin and rifampin. The clofazimine was held, as there were no available guidelines for drug administration through a nonoral route. One week post-transplant, blood and bronchoalveolar lavage (BAL) cultures were obtained for evaluation of fever; 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 (~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 postadministration (published reference range, 0.5–2 mcg/mL) [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 1 day before reducing clofazimine dose were subsequently reported at 0.62 mcg/mL at 2 hours and 0.79 mcg/mL

Received 7 February 2020; editorial decision 12 May 2020; accepted 20 May 2020.

Correspondence: Ethan Valinetz, MD, University of Washington, Box 356423, 1959 NE Pacific Street, Seattle, WA 98195 (edval89@gmail.com).

Open Forum Infectious Diseases®

DOI: 10.1093/ofid/ofaa183

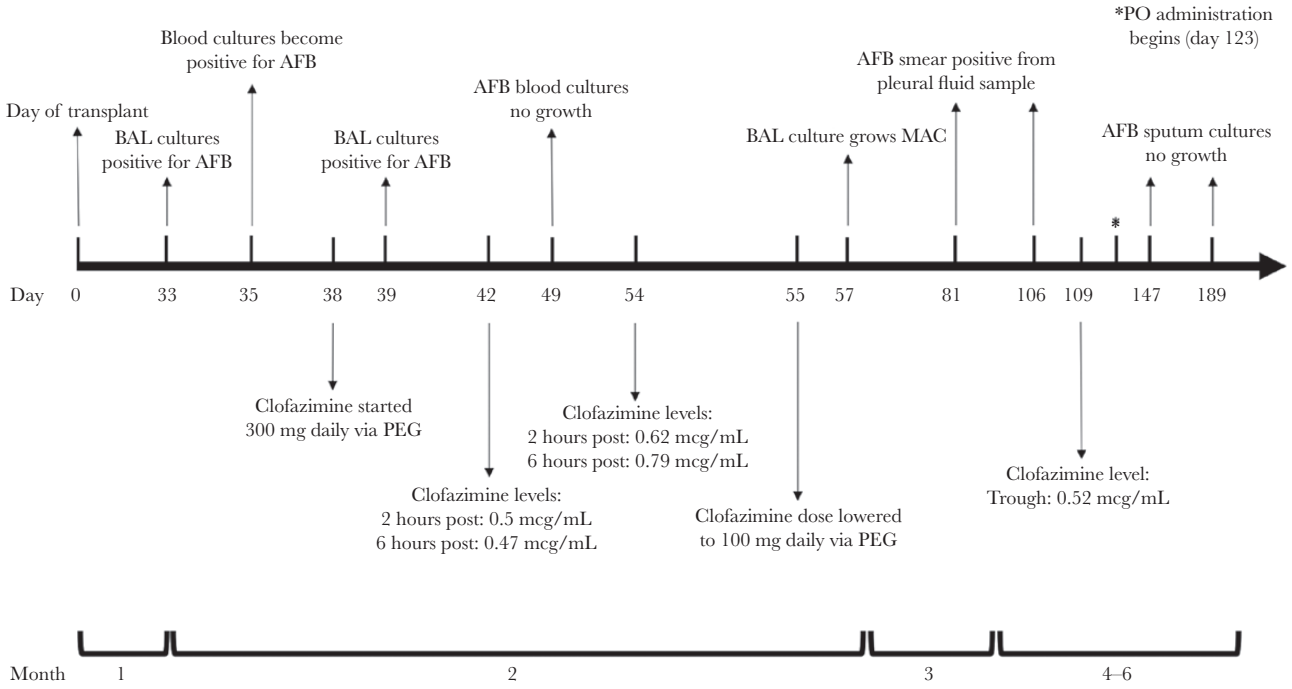

Figure 1. Summary of clinical course. Figure 1 shows a summary of the patient's clinical course with relevant microbiologic data and clofazimine start dates, dosing, and serum concentration levels. Abbreviations: AFB, acid fast bacilli; BAL, bronchoalveolar lavage; MAC, *Mycobacterium avium* complex; PEG, percutaneous endoscopic gastrostomy; PO, per os (oral).

at 6 hours postadministration. 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 before 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. Nontuberculous mycobacterial infections are a significant cause of morbidity and mortality, particularly in immunocompromised patients such as solid organ transplant recipients [13, 14]. Treatment regimens can be complex, and antimicrobials can be difficult to tolerate [15, 16]. 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 [13, 16, 17].

Clofazimine is a highly lipophilic drug with extensive tissue distribution through accumulation in macrophages and adipose cells. Absorption after oral administration of clofazimine is variable (45%–62%) and may be increased through concomitant food intake [18, 19]. Although the pharmacokinetics of clofazimine have only been partially elucidated, the reported half-life elimination of clofazimine is ~70 days, and steady state concentration is achieved at 1 month [2, 20]. In the United States, clofazimine is available via Investigational New Drug Application to the FDA, with medication supplied by the 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

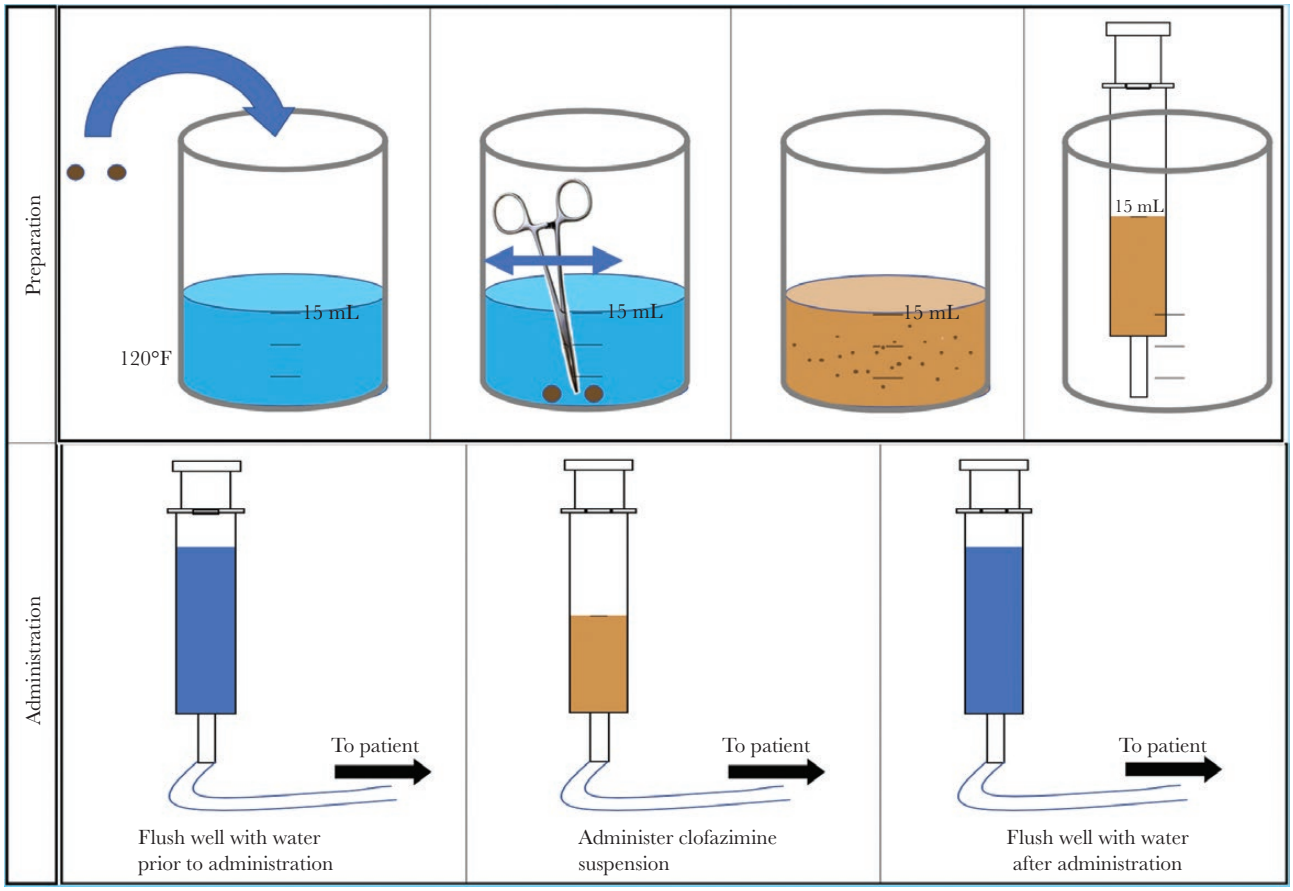

Figure 2. Preparation and administration of clofazimine suspension. Figure 2 demonstrates the preparation (top panels) and administration (lower panels) of clofazimine suspension. For preparation, fill the dose cup with 15 mL of hot water from an instant hot water dispenser (120°F) and add clofazimine capsules. Macerate with hemostat to form a slurry. Draw up slurry for administration. Put on gloves before administration to prevent staining. Flush feeding tube with water before 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.

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 extrapulmonary 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 increase to 150 mg daily [5]. In this immunosuppressed patient with mycobacteremia and unclear dose delivery and absorption, we opted to initiate clofazimine at a dose of 300 mg daily (5.4 mg/kg/d). Although the dose was considerably higher than recommended in the package insert, it was also unclear how much of the clofazimine would be delivered and 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 [12]. To optimize clofazimine use while minimizing toxicity, we measured serum concentrations to ensure that clofazimine was absorbed before reducing the dose to 100 mg daily (1.79 mg/kg/d). After 54 days of therapy, we measured her trough level to ensure that her serum concentration was not significantly elevated as 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 are uncertain. However, in our patient, clofazimine drug monitoring provided reassuring information regarding systemic absorption.

There are multiple novel formulations of clofazimine currently under investigation [7–9, 21–23]. For instance, clofazimine can be processed to a dry powder for inhaled administration [8]. Inhaled clofazimine has been shown to reduce colony counts of *Mycobacterium tuberculosis* in the lungs more significantly than oral clofazimine administration [9, 10]. Not surprisingly, inhaled clofazimine was inferior to systemic clofazimine at clearing nontuberculous mycobacterial infections in the liver and spleen in 1 study [10]. Another clofazimine formulation can be prepared in a lipid-based solution via flash nanoprecipitation technology, although this formulation has not been tested in

vivo [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 mice treated with intravenous clofazimine [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 [22]. These studies are encouraging for the future use of alternative routes of clofazimine for the treatment of nontuberculous 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.

Acknowledgments

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.

Financial support. This work was supported by the University of Washington Host Defense Research Training Grant (T32AI007044, E.D.V.), the Developmental Award from University of Washington Sexually Transmitted Infections Cooperative Research Center (U19AI11317, H.S.K.), and Research Supplement to Promote Diversity in Health-Related Research Program, National Cancer Institute at the National Institutes of Health (R01 CA213130-S, H.S.K.).

Potential conflicts of interest. None to disclose. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. Lamprene (clofazimine). Package insert. Novartis Pharmaceuticals Corporation; **1986**.
2. McGuffin SA, Pottinger PS, Harnisch JP. Clofazimine in nontuberculous mycobacterial infections: a growing niche. Open Forum Infect Dis **2017**; 4:XXX–XX.
3. Luo J, Yu X, Jiang G, et al. In vitro activity of clofazimine against nontuberculous mycobacteria isolated in Beijing, China. Antimicrob Agents Chemother **2018**; 62:e00072-18.
4. Cariello PF, Kwak EJ, Abdel-Massih RC, Silveira FP. Safety and tolerability of clofazimine as salvage therapy for atypical mycobacterial infection in solid organ transplant recipients. Transpl Infect Dis **2015**; 17:111–8.
5. Martiniano SL, Wagner BD, Levin A, et al. Safety and effectiveness of clofazimine for primary and refractory nontuberculous mycobacterial infection. Chest **2017**; 152:800–9.
6. Anjan S, Morris MI. Nontuberculous mycobacteria in solid organ transplant. Curr Opin Organ Transplant **2019**; 24:476–82.
7. Banaschewski B, Hofmann T. Inhaled antibiotics for mycobacterial lung disease. Pharmaceutics **2019**; 11:352.
8. Brunaugh AD, Jan SU, Ferrati S, Smyth HDC. Excipient-free pulmonary delivery and macrophage targeting of clofazimine via air jet micronization. Mol Pharm **2017**; 14:4019–31.
9. Verma RK, Germishuizen WA, Motheo MP, et al. Inhaled microparticles containing clofazimine are efficacious in treatment of experimental tuberculosis in mice. Antimicrob Agents Chemother **2013**; 57:1050–2.
10. Banaschewski B, Verma D, Pennings LJ, et al. Clofazimine inhalation suspension for the aerosol treatment of pulmonary nontuberculous mycobacterial infections. J Cyst Fibros **2019**; 18:714–20.
11. Koegelenberg CF, Nortje A, Lalla U, et al. The pharmacokinetics of enteral antituberculosis drugs in patients requiring intensive care. S Afr Med J **2013**; 103:394–8.
12. van Ingen J, Egelund EF, Levin A, et al. The pharmacokinetics and pharmacodynamics of pulmonary *Mycobacterium avium* complex disease treatment. Am J Respir Crit Care Med **2012**; 186:559–65.
13. Daley CL. *Mycobacterium avium* complex disease. Microbiol Spectr **2017**; 5.
14. Daley CL. Nontuberculous mycobacterial disease in transplant recipients: early diagnosis and treatment. Curr Opin Organ Transplant **2009**; 14:619–24.
15. Griffith DE, Aksamit T, Brown-Elliott BA, et al; ATS Mycobacterial Diseases Subcommittee; American Thoracic Society; Infectious Disease Society of America. An official ATS/IDSA statement: diagnosis, treatment, and prevention of nontuberculous mycobacterial diseases. Am J Respir Crit Care Med **2007**; 175:367–416.
16. Jarand J, Davis JP, Cowie RL, et al. Long-term follow-up of *Mycobacterium avium* complex lung disease in patients treated with regimens including clofazimine and/or rifampin. Chest **2016**; 149:1285–93.
17. Harrington JS, Zappetti D. Treatment of *Mycobacterium avium* complex lung disease with clofazimine. Clin Pulm Med **2016**; 23:237–238.
18. Nix DE, Adam RD, Auclair B, et al. Pharmacokinetics and relative bioavailability of clofazimine in relation to food, orange juice and antacid. Tuberculosis (Edinb) **2004**; 84:365–73.
19. Cholo MC, Mothiba MT, Fourie B, Anderson R. Mechanisms of action and therapeutic efficacies of the lipophilic antimycobacterial agents clofazimine and bedaquiline. J Antimicrob Chemother **2017**; 72:338–53.
20. Gopal M, Padayatchi N, Metcalfe JZ, O'Donnell MR. Systematic review of clofazimine for the treatment of drug-resistant tuberculosis. Int J Tuberc Lung Dis **2013**; 17:1001–7.
21. Salim M, Ramirez G, Clulow AJ, et al. Solid-state behavior and solubilization of flash nanoprecipitated clofazimine particles during the dispersion and digestion of milk-based formulations. Mol Pharm **2019**; 16:2755–65.
22. Murashov MD, Diaz-Espinosa J, Lalone V, et al. Synthesis and characterization of a biomimetic formulation of clofazimine hydrochloride microcrystals for parenteral administration. Pharmaceutics **2018**; 10:238.
23. Peters K, Leitzke S, Diederichs JE, et al. Preparation of a clofazimine nanosuspension for intravenous use and evaluation of its therapeutic efficacy in murine *Mycobacterium avium* infection. J Antimicrob Chemother **2000**; 45:77–83.