Use of inhaled imipenem/cilastatin in pediatric patients with cystic fibrosis: A case series

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ABSTRACT

Mycobacterium abscessus is a rapidly-growing, virulent, non-tuberculous mycobacterium that causes progressive inflammatory lung damage and significant decline in lung functionin patients with cystic fibrosis. *M. abscessus* complex pulmonary infections are notoriously difficult to treat, and while many antibiotics are approved for children, drug allergies or intolerances can prohibit their use. Intravenous imipenem/cilastatin is among the preferred antibiotics for treatment of *M. abscessus*, however, its use may result in systemic toxicities including hepatic injury and gastrointestinal effects. Case reports document the successful use of inhaled imipenem/cilastatin in adult cystic fibrosis and non- cystic fibrosis patients with non- *M. abscessus* pulmonary infections. To our knowledge, similar evidence does not exist for pediatric patients. In this case series, we describe two pediatric patients with cystic fibrosis and previous intolerance or lack of response to standard therapies who received inhaled imipenem/cilastatin for the treatment of chronic *M. abscessus* infection.

1. Introduction

Non-tuberculous mycobacteria (NTM) are pathogens capable of causing chronic pulmonary infection in patients with cystic fibrosis (CF). Rapid-growing *M. abscessus* complex (MABSC) are prevalent in the pediatric CF population, are notoriously difficult to treat, and are associated with greater morbidity, mortality, and accelerated decline in lung function [1].

Despite the clinical significance of MABSC pulmonary infections, randomized clinical trial data to guide therapy are lacking [1]. Current guidelines recommend a two-phase approach to treatment of NTM infections [1]. An initial intensive phase includes therapy with at least two intravenous (IV) antibiotics (typically amikacin in combination with cefoxitin, imipenem/cilastatin (IMI/CIL), or tigecycline) plus an oral macrolide. A continuation phase follows and typically includes inhaled amikacin, an oral macrolide, and two to three additional antibiotics. However, effective continuation therapy is constrained by several factors including a limited number of antibiotics with activity against MABSC, relatively high prevalence of antibiotic resistance within MABSC strains, and substantial drug toxicities. Therefore, there is a need for novel approaches to antimicrobial treatment of MABSC that can be utilized as part of continuation therapy.

IMI/CIL, a carbapenem antibiotic, provides broad coverage against several pathogens commonly isolated from sputum cultures of pediatric CF patients including methicillin-sensitive *Staphylococcus aureus* (MSSA), *Pseudomonas* spp., *Acinetobacter* spp., *Achromobacter* spp., and many NTM including MABSC. In combination with IV amikacin and an oral macrolide, IV IMI/CIL is a mainstay of MABSC intensive phase treatment [1]. However, significant nausea and vomiting can occur with IV use, making prolonged administration difficult. Inhalation of the IV drug, though not FDA approved, may offer an alternative to IV use. Case reports have documented increased drug delivery to the site of infection as well as improvement in FEV1 in adult CF and non-CF patients with non-MABSC pulmonary infections when treated with inhaled IMI/CIL [2–4]. However, similar literature does not exist in pediatric patients. The purpose of this case series is to describe the use and efficacy of inhaled IMI/CIL in two pediatric patients with CF who previously trialed several multi-drug regimens for chronic MABSC.

2. Case 1

A 16-year-old female (genotype F508del/F508del) with recalcitrant MABSC initiated inhaled IMI/CIL 250 mg (mg) twice daily in June 2017. She was previously on rotating therapies since August 2012 with persistently positive cultures, significant decline in lung function, and difficulty maintaining weight. Previously trialed therapies (with reason for discontinuation) include cefoxitin (hives), linezolid (peripheral

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neuropathy), tigecycline and clarithromycin (nausea, poor appetite), IV amikacin (hearing loss), and IV IMI/CIL (nausea) (Fig. 1A).

Due to lack of efficacy, adverse reactions, and frequent need for IV antibiotics (four cycles over 12 months), treatment with inhaled IMI/CIL was trialed. An in-clinic test dose was given under physician and pharmacist supervision and was tolerated without incident. Medication was prepared by reconstituting 500 mg IMI/CIL with 10 mL of sodium chloride 0.9%, then withdrawing 5 mL (250 mg) for the patient's dose. At this time, her regimen consisted of IV IMI/CIL and amikacin and oral clofazamine and minocycline. Upon successful toleration of inhaled IMI/CIL, her regimen was changed to the inhaled formulation, oral clofazamine, and tedizolid. She was successfully maintained on this non-IV regimen for seven months before requiring a two-month course of IV antibiotics. The aforementioned non-IV regimen was then resumed and sustained for another seven-month period, at which time she received a one-month cycle of IV antibiotics. Non-IV therapy was again resumed in December 2018, which she remains on at this time (total duration on inhaled IMI/CIL = 16 months).

She continues to tolerate this inhaled formulation with no reported side effects. Her lung function remains stable to improved, with average % predicted FEV_1 39 ± 8.4% the year before inhaled IMI/CIL vs. 44 ± 2.4% over the year post treatment (Fig. 1B). After initiation of inhaled IMI/CIL, sputum cultures remained persistently positive, which is consistent with her cultures prior to IMI/CIL initiation as well. An attempt to measure sputum IMI/CIL concentrations was made at treatment initiation but she was unable to expectorate sputum following an in-clinic IMI/CIL inhalation.

3. Case 2

A 13-year-old male (genotype F508del/F508del) with chronic MABSC began treatment with inhaled IMI/CIL at 250 mg twice daily after five years of nearly continuous therapy with various antibiotics. Previously trialed agents include inhaled and IV amikacin, cefoxitin, IV IMI/CIL (nausea, elevated liver enzymes), tedizolid, linezolid (cytopenias), and minocycline (Fig. 1A). Response was inadequate as lung function failed to improve, positive cultures persisted, and intermittent systemic side effects occurred. A trial of clofazamine was declined because of concern for potential skin discoloration.

Inhaled IMI/CIL therapy was initiated in April 2018, with dose prepared similarly to the first patient, and continued in conjunction with oral azithromycin and linezolid. Since beginning IMI/CIL therapy, the patient has maintained stable lung function (average % predicted FEV_1 72 ± 5.2% one year before inhaled IMI/CIL vs. 74 ± 0.7% in six months since starting treatment) and continues to tolerate therapy without complications (Fig. 1B). He reports improved exercise tolerance,

A

	Anti-M. abscessus Antibiotic Reactions	Dose & Administration	IV antibiotic cycles	IV antibiotic-free interval(s)
Case 1 16 years	• Cefoxitin: hives • Tigecycline: nausea, poor appetite • Clarithromycin: nausea, poor appetite • Linezolid: peripheral neuropathy • Amikacin (IV): hearing loss • Imipenem/cilastatin (IV): N/V	250 mg twice daily	2	7 months and 7 months
Case 2 13 years	• Imipenem/cilastatin (IV): nausea, elevated liver enzymes • Linezolid: cytopenias	250 mg twice daily	0	9 months

B

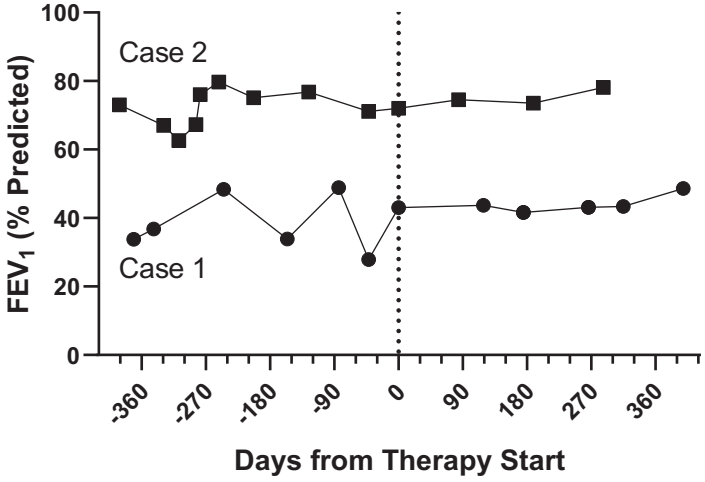

Fig. 1. 1A. Summary of cases, including reactions to prior MABSC therapies, dose of inhaled IMI/CIL utilized, IV antibiotic cycles and IV antibiotic-free interval(s since initiating inhaled IMI/CIL. IB. FEV1 in the one year prior to and since initiating inhaled IMI/CIL, demonstrating a stabilization of lung function after addition of inhaled IMI/CIL.

improvement in cough symptoms, and has remained off IV antibiotics for 9 months. Sputum and bronchoscopy cultures after initiation of inhaled IMI/CIL remained persistently positive, similar to his history prior to starting this therapy, although the patient anecdotally reported a decrease in overall sputum production.

Six months into inhaled IMI/CIL therapy, sputum was obtained 15 min after drug inhalation, diluted in 5 mL buffered saline per gram, and supernatant recovered using standard methods [5]. Drug in sputum supernatant were determined using a previously described mass spectrometric method modified to add selected reaction monitoring conditions for IMI (m/z 300.3➔126.1) and CIL (m/z 359.3➔202.1), with concentrations calculated by comparison to spiked samples run in parallel. Estimated drug concentrations were ~25 μg/mL for IMI and 75 μg/mL for CIL.

4. Discussion

IMI/CIL, a carbapenem antibiotic, is an effective agent against MABSC when administered IV, but the efficacy of alternative routes of administration has not been well studied. Varying levels of success in treating assorted pulmonary infections have been reported with inhalation of IV preparations of antibiotics, including IMI/CIL, in adult CF and non-CF patients. However, there are no similar case reports or studies in pediatric patients. At our center, two pediatric CF patients with documented MABSC pulmonary infections continue to receive inhaled IMI/CIL. Both patients have tolerated several months of inhaled IMI/CIL without reported side effects and with sustained stable lung function. This has allowed for longer IV antibiotic-free intervals, reduced overall exposure to systemic side effects experienced with previous therapies, and presumably increased quality of life. Sputum drug concentrations measured in one patient were somewhat below previous reports [5], though still above measured minimal inhibitory concentrations. Our experience suggests that in pediatric CF patients with chronic MABSC pulmonary infections, inhaled IMI/CIL may provide another treatment alternative.

Conflict of interest statement

There are no conflicts of interest.

Declarations of interest

None.

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