Use of telavancin in adolescent patients with cystic fibrosis and prior intolerance to vancomycin: A case series

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Abstract

The most common pathogen in pediatric cystic fibrosis (CF) patients is *Staphylococcus aureus*, and drug-resistant species are associated with negative outcomes. Methicillin-resistant *Staphylococcus aureus* (MRSA) is notoriously hard to treat because many antibiotics are not FDA approved for children and drug allergies or intolerances can prohibit the use of others. Telavancin is currently indicated for hospital-acquired pneumonia and ventilator-associated pneumonia caused by MRSA, but it has not been studied in patients with CF or in pediatrics. As a semi-synthetic derivative of vancomycin, it is unknown if cross-reactivity with telavancin occurs in patients with vancomycin hypersensitivity or intolerance. In this case series, we describe three adolescent patients with CF and previous intolerance to vancomycin who received telavancin for bronchopulmonary exacerbations.
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1. Introduction

The most common pathogen among pediatric patients with cystic fibrosis (CF) is *Staphylococcus aureus* [1]. Unlike the rates of *Pseudomonas aeruginosa*, which have been steadily declining over time, the prevalence of methicillin-resistant *Staphylococcus aureus* (MRSA) infections increased dramatically in the early 21st century and has remained steady at approximately 25% over the past five years [1]. While MRSA prevalence peaks between 18 and 24 years of age, this pathogen is frequently detected in young children, putting these patients at risk of decreased lung function and increased mortality associated with chronic MRSA infection [1,2]. Unfortunately, pediatric patients with CF have few evidence-based treatment options, as many anti-MRSA agents are not FDA-approved for patients less than 18-years of age. Hypersensitivity or intolerance to approved parenteral therapies may also preclude the use of currently approved agents. Telavancin (Vibativ®), a lipoglycopeptide antibiotic, is indicated for adults with complicated skin and skin structure infections as well as hospital-acquired and ventilator-associated bacterial pneumonia caused by susceptible organisms, including MRSA [3]. As a semi-synthetic derivative of vancomycin, telavancin poses a potential risk of hypersensitivity reactions and Redman Syndrome in patients who previously reacted to vancomycin; however, the rate of cross-reactivity is not well-established [3]. Telavancin's utility in patients with CF is not well studied, and a survey conducted in 2013 did not identify any accredited CF centers

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prescribing it commonly for hospitalized pediatric patients with MRSA infections [2]. The purpose of this case series is to describe the single center use of telavancin for pulmonary exacerbations in three adolescent patients with CF who had documented intolerances or hypersensitivity reactions to vancomycin. To our knowledge, there are no currently published case reports documenting the use of telavancin in pediatric patients or patients with previous intolerance to vancomycin.

2. Case summaries

2.1. Case 1

A 17-year-old female (genotype F508del/E585X) with previously documented MRSA and *Pseudomonas aeruginosa* bronchopneumonia and prior reactions to vancomycin, ceftaroline, and tigecycline (Table 1) started telavancin 10 mg/kg daily after minimal clinical improvement with oral linezolid prescribed 9 days prior to admission. For the first dose of telavancin, she received 10% of the total dose administered over 1 h with the plan to receive the remaining 90% if tolerated, as recommended by the allergy and immunology consultants. However, she developed diffuse hives and pruritus during the initial infusion that resolved by stopping the infusion and giving intravenous (IV) diphenhydramine 25 mg. Therefore, she discontinued telavancin and initiated IV linezolid as an alternative. Although she also experienced similar symptoms with the first dose of IV linezolid, she tolerated a similar test-dose of linezolid and completed approximately 18 days of therapy before discontinuing due to nausea and vomiting.

2.2. Case 2

A 17-year-old female (genotype F508del/F508del) with documented MRSA infection and previous reactions to vancomycin and ceftaroline (Table 1) developed a worsening cough with post-tussive emesis despite a two-week course of IV linezolid. She started telavancin 10 mg/kg daily administered over 60 min with oral diphenhydramine prior to each dose. She also started prednisone prior to hospitalization for an asthma exacerbation and received 30 mg daily that tapered throughout her antibiotic treatment course. She tolerated six doses of telavancin in the hospital, with the exception of experiencing a bad taste in her mouth, and discharged to finish a three-week course. She experienced chills after her fourth and fifth doses of outpatient therapy and an extra dose of clonazepam 0.25 mg, which she already received for anxiety, was scheduled prior to future doses of telavancin. The chills

Table 1
Case summaries.

Patient	Age	Anti-MRSA antibiotic reactions	Dose & administration	Start SCr	End SCr	Start FEV_1	End FEV_1	Completed therapy
				(mg/dL)		*(% Predicted)*		
Case 1	17	• Vancomycin: oropharyngeal pruritus, cutaneous eruption, RMS • Ceftaroline: maculopapular rash, serum sickness • Tigecycline: pruritic rash, N/V	10 mg/kg daily (450 mg) Test-dose: 10% of total dose given over 60 min	0.51	N/A	29	N/A	No *
Case 2	17	• Vancomycin: RMS, tingling, hives, rash • Ceftaroline: Delayed cutaneous reaction	10 mg/kg daily (700 mg) Given over 60 min Pretreated with PO diphenhydramine 50 mg (IP) and 75 mg (OP)	0.66	0.63	55	58	Yes
Case 3 (1st course)	12	• Vancomycin: RMS despite administration as CIV, hives • Minocycline: Hives • Ceftaroline: Hives, angioedema of face and extremities • Linezolid: Neuropathy	10 mg/kg daily (522 mg) Given over 60 min Pretreated with PO acetaminophen 650 mg, PO diphenhydramine 25 mg	0.46	0.47	96	102	Yes
Case 3 (2nd course)	13	• Vancomycin: RMS despite administration as CIV, hives • Minocycline: Hives • Ceftaroline: Hives, angioedema of face and extremities • Linezolid: Neuropathy	8.7 mg/kg daily (500 mg) Given over 60 min Pretreated with PO acetaminophen 500-650 mg, diphenhydramine 25 mg	0.45	0.54	97	93	No **
Case 3 (3rd course)	13	• Vancomycin: RMS despite administration as CIV, hives • Minocycline: Hives • Ceftaroline: Hives, angioedema of face and extremities • Linezolid: Neuropathy	10 mg/kg daily (540 mg) Given over 90 min Pretreated with PO/IV diphenhydramine 25 mg	0.52	0.53	83	85	No ***

IP: Inpatient; OP: Outpatient; PO: Oral; IV: Intravenous; CIV: Continuous Intravenous Infusion; RMS: Redman Syndrome; N/V: Nausea and vomiting

* Experienced itching during test dose that resolved by stopping infusion and giving diphenhydramine.

** Family noted patient missed final dose due to hives.

*** Switched therapy after four doses due to lack of FEV_1 response.

resolved and she completed the full three weeks of therapy without further adverse effects. Her serum creatinine (SCr) remained stable throughout therapy (Table 1). Her forced expiratory volume in 1 s (FEV_1) was 55% prior to therapy and improved to 58% at initial follow-up 11 days after therapy completed (Table 1). This was documented as her highest FEV_1 recorded in the past year.

2.3. Case 3

A 12-year-old female (genotype G551D/F508del) on ivacaftor with documented MRSA and *Pseudomonas aeruginosa* infections, and previous reactions to vancomycin, minocycline, ceftaroline, and linezolid (Table 1) received three courses of telavancin over a 10-month period. The first course was initiated during a hospitalization for a CF pulmonary exacerbation. Telavancin 10 mg/kg daily was administered over 60 min with oral acetaminophen and diphenhydramine given prior to doses. She also started oral ciprofloxacin and inhaled tobramycin to treat *Pseudomonas aeruginosa* at that time. She had mild facial flushing after the first dose of telavancin, but tolerated five doses administered in the hospital and her cough improved. She discharged and completed a 16-day course. Her SCr remained stable and FEV_1 increased from 96% of predicted on day of admission to 102% of predicted 1 week after finishing therapy (Table 1).

During a subsequent hospitalization five months later, she started a second course of telavancin at a dose rounded to an even vial quantity of 8.7 mg/kg daily. Her cultures were only positive for MRSA at this time. She received two doses while inpatient and was discharged to finish a two week course in the outpatient setting. Her family noted she experienced hives at the end of therapy causing her to miss her final dose, though this was not confirmed by a medical provider. Her SCr remained stable throughout therapy, but FEV_1 declined from 97% predicted prior to therapy to 93% predicted on day of therapy completion (Table 1). Cultures obtained at that time were newly positive for *Aspergillus fumigatus*.

A third course of telavancin in addition to oral voriconazole occurred during a hospitalization four months later. She received telavancin 10 mg/kg daily and tolerated four doses despite pruritus without hives before switching to tigecycline due to an inadequate response in lung function. Her renal function remained stable while receiving telavancin (Table 1).

3. Discussion

Telavancin, a lipoglycopeptide antibiotic, is an effective agent against MRSA in the adult population, but has not been studied in pediatrics yet. An initial phase III trial of telavancin excluded patients with CF, so efficacy in this population requires further exploration [4]. At our center, three adolescent patients with CF and documented intolerance to vancomycin received telavancin on five different occasions. Two patients tolerated full courses of telavancin at doses of 10 mg/kg daily administered over 60 min and safely received telavancin in the outpatient setting as well. FEV_1 improved in two cases of telavancin use. Patients should be monitored for cross-reactivity as one patient with a previous IgE-mediated reaction to vancomycin did not tolerate a test dose of telavancin. Telavancin can cause nephrotoxicity, but each patient's renal function remained stable during treatment [4]. Of note, no patients received concomitant nephrotoxic antibiotics, such as aminoglycosides, which are associated with exacerbating the nephrotoxicity of vancomycin [5]. Lastly, all patients were at least 12 years of age and weighed at least 45 kg. It is unknown if the dosing strategies used would be safe in younger or smaller children, but a trial evaluating the pharmacokinetics of telavancin in children ages 3 months to 17 years is underway (NCT02013141). Our experience suggests that previous intolerance, such as Redman Syndrome, to vancomycin should not prohibit a trial of telavancin with premedication and that a dose of 10 mg/kg daily administered over at least 60 min appears safe for patients weighing over 45 kg. However, patients with an IgE-mediated allergy to vancomycin may be at a higher risk of cross-reactivity.

Declarations of interest

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