

Single Case

Drug Reaction with Eosinophilia and Systemic Symptoms Syndrome following Dalbavancin and Oritavancin Administration in a Patient with Osteomyelitis

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Keywords

Adverse drug reaction · Drug eruption · Infections

Abstract

Introduction: Dalbavancin and oritavancin are newer long-acting antibiotics with potent activity against gram-positive organisms, including methicillin-resistant *Staphylococcus aureus* (MRSA). To our knowledge, there have been no reported cases of drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome in a patient treated with dalbavancin and oritavancin. **Patient Presentation:** A woman in her 20s presented with a right thumb abscess and cellulitis that failed to respond to several courses of oral antibiotics, resulting in recurrent emergency room visits over 3 weeks. Approximately 1 month after the initial skin infection, magnetic resonance imaging revealed osteomyelitis of the right thumb. She was treated with a single dose of oritavancin followed by two weekly doses of dalbavancin, which successfully resolved the infection. However, she subsequently developed fever and a rash consistent with DRESS syndrome, likely triggered by oritavancin or dalbavancin. Given the prolonged half-life of these medications, she required treatment with high-dose steroids for an extended duration. **Conclusion:** Dalbavancin and oritavancin are second-generation lipoglycopeptide antibiotics that provide coverage for gram-positive organisms, including MRSA. They are approved for the treatment of acute bacterial skin and skin structure infections and are used off-label for bacteremia, endocarditis, and osteomyelitis. Their prolonged half-lives – 257 h for dalbavancin and 195 h for oritavancin – allow for less frequent dosing.

However, a long half-life also leads to prolonged drug exposure in the event of adverse effects. Here, we report the first case of DRESS syndrome in a patient treated with dalbavancin and oritavancin.

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Introduction

Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome is a rare, potentially life-threatening hypersensitivity reaction characterized by fever, diffuse skin rash, and multi-organ involvement. Commonly associated drugs include antiepileptics, sulfonamides, NSAIDs, allopurinol, and antimicrobials; recent literature demonstrates that antibiotics are responsible for up to 74% of DRESS cases [1]. Symptoms typically occur within 2–8 weeks following administration of the offending agent [2, 3]. DRESS accounts for 10–20 percent of all cutaneous adverse drug reactions and mortality rates have been reported as high as 10% [2–4]. The Registry of Severe Cutaneous Adverse Reactions (RegiSCAR) scoring system is one of the widely used criteria that can be used to diagnose the DRESS [5].

Dalbavancin and oritavancin are bactericidal second-generation lipoglycopeptide antibiotics that interfere with cell wall synthesis. They demonstrate strong activity against gram-positive organisms, including methicillin-resistant *Staphylococcus aureus* (MRSA), methicillin-resistant coagulase-negative *Staphylococci*, and penicillin-resistant *Streptococci*. Dalbavancin and oritavancin are approved by the FDA for the treatment of acute bacterial skin and skin structure infections (ABSSSI) [6–9]. They are also effective in the treatment of other infections, including osteomyelitis [10, 11]. Compared to the earlier generation glycopeptides (vancomycin and teicoplanin), dalbavancin and oritavancin have an extended duration of action, with an approximate half-life of 196 h and 257 h, respectively [12]. These pharmacokinetic profiles allow for once-weekly dosing [6, 7, 13, 14]. We report a case of DRESS syndrome in a patient treated with dalbavancin and oritavancin for osteomyelitis.

Case Presentation

A woman in her twenties with no significant medical history presented to the emergency department (ED) with persistent painful swelling and redness of the right thumb with associated wound drainage and reduced range of motion. Before this ED presentation, she was evaluated in an urgent care several weeks prior and prescribed cephalexin. Due to a lack of symptomatic improvement, she returned to urgent care 10 days later, and the antibiotic was switched from cephalexin to trimethoprim/sulfamethoxazole. Another 10 days later, the symptoms still had not improved, and the patient presented to the ED for further evaluation.

In the ED, a plain radiograph of her right hand revealed soft tissue swelling of the right first phalanx without evidence of bony pathology. She underwent an incision and drainage of the wound, and cultures were obtained; she was then discharged home with a second course of trimethoprim/sulfamethoxazole. Three days later, the patient was called back to the ED because the wound culture revealed polymicrobial growth, including MRSA with resistance to trimethoprim/sulfamethoxazole, *Fingoldia magna*, *Peptoniphilus asaccharolyticus*, and *Prevotella* spp. The patient reported ongoing right thumb pain but was not experiencing fever or other systemic symptoms. Her physical exam was notable for tachycardia and mild edema of the right thumb with slight induration of the thumbnail; no fluctuance was appreciated. Blood cultures from

her initial ED visit 3 days ago remained negative. She received one dose of intravenous oritavancin 1.2 g, and one dose of intravenous metronidazole 500 mg. The patient was discharged home with a 7-day course of oral metronidazole as well as one dose of fluconazole 150 mg.

Several days after discharge, she underwent a follow-up hand magnetic resonance imaging which revealed marrow edema in the distal phalanx of the right thumb with surrounding cellulitis, consistent with osteomyelitis. Subsequently, she received two doses of intravenous dalbavancin 1,500 mg 1 week apart. Following the first dose, the patient developed a low-grade fever and body aches. Following the second dose of dalbavancin, she developed a daily high-grade fever of 102°F with rigors, myalgias, and bilateral knee arthralgias. She was afebrile and otherwise feeling well between these two doses of dalbavancin. Outpatient laboratory studies on the day after the second dose of dalbavancin were significant for leukopenia (WBC to 2.99) with absolute neutrophil count 1.1 and 10% eosinophils (absolute eosinophil count of 300 cells per microliter), as well as marginal elevation of alanine transaminase to 41, with all other laboratory values within normal limits. In the setting of fever, leukopenia, and transaminitis, the patient was referred to the ED for a possible drug reaction. Timeline of her presentation is summarized in Figure 1.

In the ED, the patient was noted to be febrile and to have a new-onset diffuse rash (Fig. 2). Her exam was notable for facial erythema, but no facial edema, and erythematous macules involving the trunk and extremities without mucosal involvement, bilateral occipital/periauricular adenopathy, and largely resolved right thumb erythema/swelling. Infectious diseases and dermatology services were consulted. Her presentation was thought to be most consistent with DRESS, and the patient was admitted to the hospital and started on intravenous glucocorticoids. The patient continued to have persistently high fevers to 104°F. Blood liver enzyme levels continued to uptrend. Abdominal ultrasound showed mild splenomegaly but was otherwise unremarkable. The rash continued to improve. The final diagnosis was thought to be DRESS syndrome secondary to dalbavancin and/or oritavancin, and the patient was discharged on prednisone 80 mg daily.

Differential Diagnosis

There is a heterogeneous group of cutaneous delayed T-cell-mediated hypersensitivity reactions associated with pharmacologic agents, including Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN), DRESS, acute generalized exanthematous pustulosis, generalized bullous fixed drug eruption, and simple morbilliform drug eruption [4]. Our patient presented with an erythematous maculopapular eruption. SJS/TEN typically manifests with macules that progress to vesicles or bullae, desquamation, and the characteristic involvement of mucosal surfaces, none of which were observed in our patient. Similarly, an acute generalized exanthematous pustulosis rash is characterized by sudden onset of pustules, which were also absent in this case. Her skin examination, visceral organ involvement, fevers, lymphadenopathy, and eosinophilia made DRESS the most likely diagnosis. Other diagnostic considerations included hemophagocytic lymphohistiocytosis and adult-onset Still's disease, but the patient did not meet diagnostic criteria for either of these conditions.

Outcome and Follow-Up

The patient did not require any further antibiotics or alternative antibiotics to treat her osteomyelitis since she completed treatment for her osteomyelitis with two doses of dalbavancin. The patient attended a dermatology follow-up appointment approximately 1 week

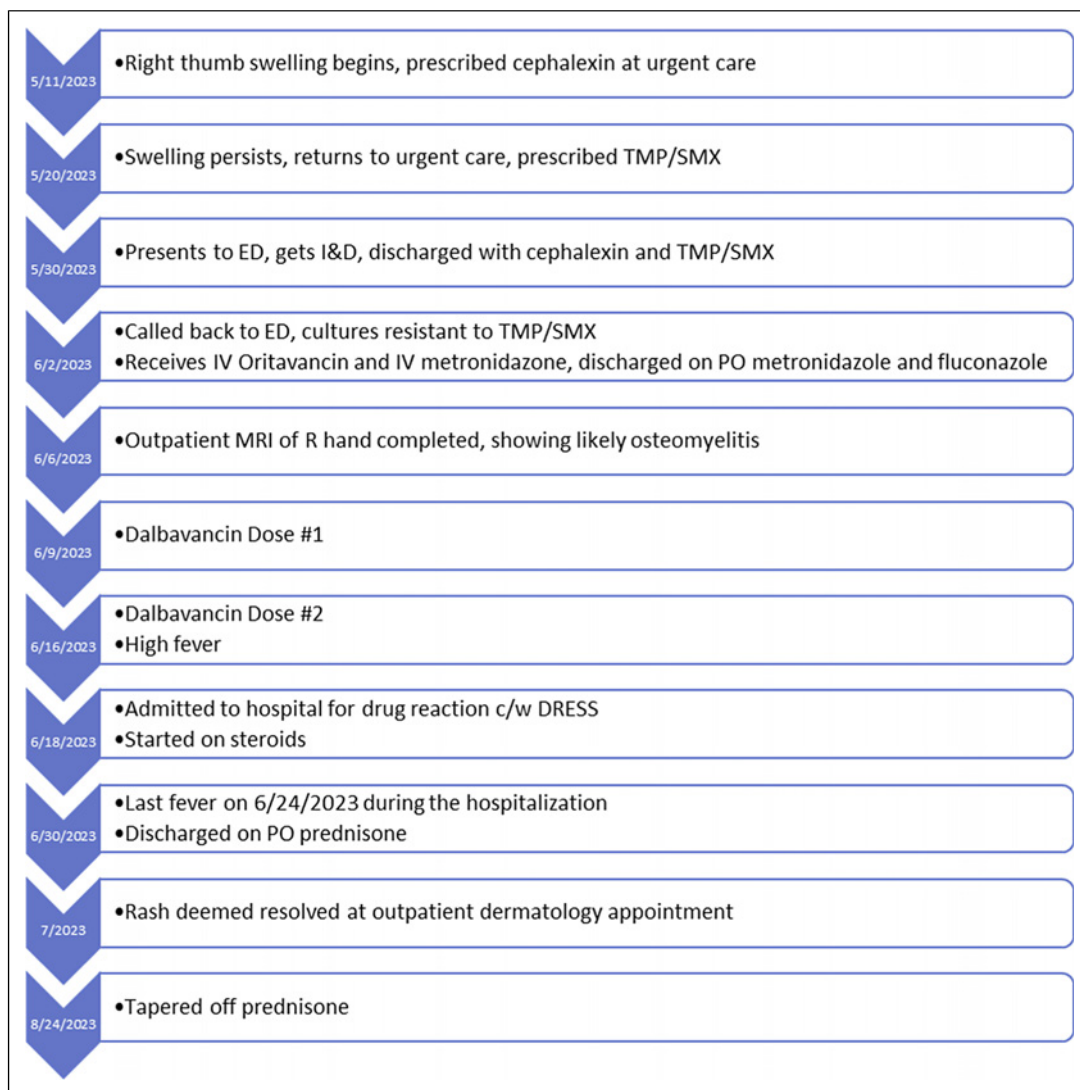


Fig. 1. Case timeline.

after discharge, at which time the rash had resolved. Various outpatient attempts were made to taper steroids, and steroid-sparing agents such as mycophenolate were introduced. However, due to the development of additional complications, the patient ultimately required a prolonged steroid taper over the course of 2 months. Both dalbavancin and oritavancin were added to her medication allergy list.

Discussion

DRESS syndrome is a complex syndrome with a broad spectrum of clinical features; its diagnosis is predominately clinical and supported by laboratory findings. The clinical manifestations are not immediate and typically appear 2–8 weeks after introduction of the triggering drug [1–3]. Common features of DRESS include fever, rash, lymphadenopathy, hematological findings (eosinophilia, leukocytosis), and abnormal liver function tests. Cutaneous manifestations, which are present in most cases, typically consist of an urticarial,



Fig. 2. Truncal and lower extremity rash in our patient.

maculopapular eruption and are rarely associated with vesicles, bullae, pustules, purpura, target lesions, facial edema, cheilitis, and erythroderma [2, 3]. Visceral involvement is the major cause of morbidity and mortality in this syndrome, which includes hepatitis, pneumonitis, myocarditis, pericarditis, nephritis, and colitis [2, 3]. There are many diagnostic criteria for DRESS syndrome in the literature. The most widely used criteria are the RegiSCAR scoring system, which is shown in Table 1 [5]. Our patient scored 6 in the RegiSCAR scoring system; a score of 5 or greater represents a definitive DRESS (Table 1). The life-threatening potential of DRESS syndrome is high and mortality is estimated to be around 10% in multiple studies [2, 3]. Presenting signs and symptoms for our patient included fever, leukopenia, and transaminitis, followed by a rash and lymphadenopathy the next day; symptom onset was about 10 days after the first dose of dalbavancin and 17 days after oritavancin. Due to the timeline above, the drugs most likely responsible for her symptoms are dalbavancin and/or oritavancin. It is also possible that trimethoprim/sulfamethoxazole could have been the causative agent as it is commonly associated with DRESS [2, 3]. However, the patient received trimethoprim/sulfamethoxazole about 1 month prior to the onset of fever, with the last dose administered 16 days before the fever. Given the half-life of trimethoprim/sulfamethoxazole is approximately 10 h, we concluded that it is less likely that this medication was the cause of DRESS. Similarly, metronidazole and fluconazole could also have been potential causative agents; however, metronidazole and fluconazole are less commonly associated with DRESS, and the timeline did not align with the onset of her symptoms.

The current understanding of the pathogenesis of DRESS is incomplete. The pathogenetic mechanism is thought to involve a T-cell-mediated drug reaction causing production of TNF- α and interferon- γ , expansion of the regulatory T-cell population, and reactivation of herpesviruses [15]. The most commonly implicated medications are anticonvulsants

Table 1. Registry of Severe Cutaneous Adverse Reactions (RegiSCAR) DRESS validation score [5]

	No	Unknown	Yes	Our patient
Fever $\geq 38.5^{\circ}\text{C}$	–1	–1	0	0
Lymphadenopathy	0	0	1	1
Eosinophilia 700–1,499/ μL or 10–19.9%	0	0	1	1
Eosinophilia $>1,500/\mu\text{L}$ or $>20\%$	0	0	2	0
Atypical lymphocytes	0	0	1	0
Skin rash $>50\%$ BSA	0	0	1	1
Skin rash suggestive of DRESS	–1	0	1	1
Biopsy suggestive of DRESS	–1	0	0	0
One organ involvement	0	0	1	1
>2 organ involvement	0	0	2	0
Resolution in >15 days	–1	–1	0	0
Exclude alternative diagnosis	0	0	1	1
Final score				
<2: no case				
2–3: possible case				
4–5: probable case				
>5 : definite case				6

(carbamazepine, phenytoin, lamotrigine), allopurinol, sulfonamide-containing antibacterials, mexiletine, minocycline, and vancomycin [2, 3]. However, among hospitalized patients, antibiotics are the most common suspected culprit medications, with vancomycin accounting for 39% [1] to 60% [11] of antibiotic-related cases of DRESS.

The prompt recognition of symptoms associated with DRESS and the removal of the causative drug are the most crucial steps in the management of DRESS syndrome. The earlier the causative agent is withdrawn, the better the prognosis [6]. An improved understanding of the culprit drugs and potential predispositions may help further identify at-risk populations and guide medication use. Corticosteroids are typically utilized to dampen the immune response in an effort to shorten the time frame of the syndrome and protect the skin and viscera.

Over the past few decades, vancomycin has emerged as an antibiotic of choice for serious MRSA infections. With the increasing frequency of vancomycin-resistant strains, the development of new antibiotics active against MRSA has been eagerly anticipated. Three new lipoglycopeptides are now available: telavancin, oritavancin, and dalbavancin. Both dalbavancin and oritavancin have longer half-lives which allow for less frequent dosing – an appealing feature likely to circumvent issues with non-adherence, as well as shorten hospitalization. Dalbavancin and oritavancin, second-generation lipoglycopeptide antibiotics, exhibit bactericidal effects by interfering with cell wall synthesis, similar to vancomycin. They have potent activity against gram-positive organisms, including MRSA. Both dalbavancin and oritavancin have been approved by the FDA for the treatment of ABSSSI [6, 7, 9]. Several studies have also shown these antibiotics to be effective for the treatment of other infections, including osteomyelitis and endocarditis [8–10]. A recent randomized clinical trial confirmed that two 1,500 mg weekly doses of dalbavancin were effective as standard care in osteomyelitis [8]. A head-to-head comparison study by Steuber et al. [16] found no significant difference in clinical success at 90 days between dalbavancin and oritavancin for complicated

infections, including osteomyelitis. However, there was a trend toward a higher incidence of adverse drug reactions with oritavancin compared to dalbavancin, which led to more treatment discontinuations.

Compared to the earlier glycopeptides, dalbavancin and oritavancin have an extended duration of action, which allows for once-weekly dosing [6, 7, 9, 14]. The route of metabolism of dalbavancin and oritavancin is unknown; they are not cytochrome-P450 inhibitors, substrates, or inducers. Clinical trials of dalbavancin and oritavancin have shown a comparable safety profile and similar drug-related adverse events compared to standard-of-care antibiotics [6, 7, 9]. A narrative review of seven randomized controlled clinical trials showed no difference in adverse effects (AE) between dalbavancin and comparators [7]. The most reported AEs of dalbavancin are gastrointestinal symptoms, infusion reactions, and hypersensitivity reactions [7, 14]. The most common adverse reactions ($\geq 3\%$) in patients treated with oritavancin were headache, nausea, vomiting, limb and subcutaneous abscesses, and diarrhea [13]. A few cases of hypersensitivity, an anaphylactoid reaction, and a case of SJS have been described in the literature in association with dalbavancin therapy and TEN reported with oritavancin [13]. Although no clear cross-reactivity was demonstrated between vancomycin and dalbavancin/oritavancin, caution is recommended in the administration of dalbavancin or oritavancin to patients with a history of anaphylaxis to glycopeptides [12–14].

Here we report a case in which a patient was diagnosed with DRESS syndrome after receiving dalbavancin and oritavancin for osteomyelitis. To date, there have been no reported cases of dalbavancin or oritavancin-associated DRESS syndrome. As mentioned above, vancomycin is frequently associated with DRESS, which is the related first-generation glycopeptide antibiotic, though cross-reactivity between vancomycin, dalbavancin, and oritavancin is not well known. Compared to vancomycin, dalbavancin and oritavancin have a longer half-life and thus extended duration of action, raising the risk of prolonged duration of AEs. Our patient required a 2-month-long steroid taper. The patient was advised to avoid both dalbavancin and oritavancin in the future. In the case of DRESS syndrome and its potentially life-threatening side effects, the prompt recognition of its clinical features and discontinuation of the causative agent are critical, especially if the potential causative agent has a long half-life.

Conclusion

Dalbavancin and oritavancin are second-generation lipoglycopeptide antibiotics providing coverage for gram-positive organisms, including MRSA. Both dalbavancin and oritavancin are approved for treatment of ABSSSI. Studies examining off-label use of dalbavancin and oritavancin show positive results for use in difficult-to-treat infections (e.g., endocarditis, osteomyelitis). Providers should be aware of rare but life-threatening side effects, such as SJS/TEN and DRESS, when utilizing a drug with a prolonged half-life, such as dalbavancin and oritavancin. While logistically advantageous in the clinical setting, the prolonged half-life of these drugs can potentially raise the risk of an allergic reaction of prolonged duration. The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see <https://doi.org/10.1159/000545359>).

Statement of Ethics

Ethical approval is not required for this study in accordance with local or national guidelines. Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Jina Bai: data collection, literature review, and manuscript writing. Nina Blank: literature review and manuscript editing. Mary Baxter Harlow: manuscript editing. Emily Frech Preciado: manuscript editing and drawing of diagrams.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further enquiries can be directed to the corresponding author.

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