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Case report

Fever for days: A challenging case of dalbavancin-induced fever

Mohamed A. Almahal [a], Claire Wan [a], Benjamin Albrecht [a], Sarah Green [a], Ahmed Babiker [b,*]

[a] Division of Infectious Diseases, Department of Medicine, Emory University School of Medicine, Atlanta, GA, USA
[b] Division of Infectious Diseases, Department of Internal Medicine, Rush University Medical Center, Chicago, IL, USA

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ABSTRACT

Dalbavancin is a novel long acting lipoglycopeptide antibiotic with a favorable safety profile approved for treating Acute Bacterial Skin and Skin Structure Infections (ABSSSI) caused by Gram-positive organisms. Given its long half-life, a two-dose regimen can provide effective systemic therapy for up to six weeks, making it an appealing option to avoid prolonged intravenous antibiotic therapy. Herein, we report a case of a 27-year-old male who developed dalbavancin-induced fever while treating Methicillin-sensitive *Staphylococcus aureus* (MSSA) bacteremia. Despite being inconsistently reported, our case highlights fever as a possible side effect of dalbavancin therapy, and the challenging management of this adverse event given its prolonged half-life.

Introduction

Dalbavancin is a novel long acting lipoglycopeptide with potent activity against Gram-positive organisms and a favorable safety response [1]. In 2014, it was approved for use in Acute Bacterial Skin and Skin Structure Infections (ABSSSI) caused by Gram-positive pathogens [2]. Given its long half-life, pharmacokinetic modeling indicates that a two-dose regimen can provide effective systemic therapy for up to 6 weeks, making it an appealing option to avoid prolonged IV therapy and reduce the need for extended hospitalization for deep-seated and osteoarticular infections [3]. Phase II and III studies have demonstrated that Dalbavancin is generally well tolerated with a better safety profile than common comparators [4]. However, uncertainty exists on how to manage adverse events given its long half-life [5]. Herein, we report a person who inject drugs who developed a high-grade fever following dalbavancin therapy.

Case report

A 27-year-old male with a history of hemophilia and polysubstance use (actively using intravenous (IV) methamphetamines), was transferred to our Emergency Department with a painful, swollen right knee and left elbow following a motor vehicle collision 2 days prior. At an outside hospital, he underwent several computed tomography (CT) scans (head, C-spine, chest, abdomen, and knee) which were normal except for the finding of right knee hemarthrosis. Given his history of hemophilia, he was transferred to our center for factor VIII infusion. On day 4 following his admission, the patient developed a high-grade fever. Given his hemarthrosis, he was evaluated for possible septic arthritis. Joint aspiration performed by an orthopedic surgeon was negative for septic arthritis (nucleated cell count: 1828 (93 % neutrophils), Gram-stain and culture negative, no crystals). The infectious disease service was consulted, examination revealed erythema and induration around a peripheral IV in his right forearm, consistent with thrombophlebitis. Blood cultures were drawn, and the patient was stared on empiric vancomycin and cefazolin when initial blood culture was reported as positive for *Staphylococcus aureus* [6]. Transthoracic echocardiography and transesophageal echocardiography were performed, which showed no evidence of infective endocarditis. Subsequently antimicrobial susceptibility testing revealed the isolate to be methicillin sensitive *Staphylococcus aureus* (MSSA) and his antimicrobial therapy was streamlined to cefazolin monotherapy. Repeated blood cultures were drawn and were negative.

The patient expressed a strong desire to leave the hospital due to caregiving responsibilities at home. Given his ongoing IV methamphetamine use, the infectious diseases team was hesitant to discharge him with a central line for outpatient IV antibiotics. Similarly, given the risk of serotonin syndrome with linezolid and methamphetamines, this step down to oral linezolid was avoided. Thus, after 14 days of IV therapy from blood culture clearance he was given a dose of dalbavancin

* Corresponding author.
E-mail address: Ahmed_babiker@rush.edu (A. Babiker).

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with plans for double coverage with PO cefadroxil to complete a four-week course of therapy from blood culture clearance for MSSA bacteremia and thrombophlebitis [7]. Within 24 hours of dalbavancin administration, the patient developed a persistent high-grade fever and left retro-orbital pain. Extensive workup for a healthcare-associated infection and/or a deep-seated *S. aureus* seeding was performed, which included serial physical examinations, complete blood count with differential, Chest X-rays, CT scans of the chest, abdomen and orbit, and blood cultures, all of which were unremarkable. The patient was managed with antipyretics and the team considered starting steroids. However, the patient left against medical advice four days after fever onset, which was still persistent at the time of departure. He was later seen in the Infectious Disease clinic 3 weeks following discharge. His fever had abated after seven days total per his report, and he was asymptomatic. He has since continued to follow up with hematology with no further issues. Given the timing of fevers relative to the dalbavancin administration (prior to starting cefadroxil) and the lack of positive findings on work-up for an alternative cause, a dalbavancin-induced fever was suspected. This led to a Naranjo Adverse Drug Reaction (ADR) Probability Scale score of six (probable).

Discussion

Here we present a 27-year-old male who developed a fever after receiving a dose of dalbavancin for MSSA bacteremia. Although a healthcare-associated infection or a deep-seated MSSA infection were possible explanations, the patient's investigations ruled these out as possibilities, thus raising our suspicion of dalbavancin-induced fever which is supported by his high Naranjo ADR score.

Fever has been inconsistently reported across the literature, with no fever reported in a large, pooled analysis [4]. In contrast, in phase I trial, pyrexia was reported as the most frequent adverse event among adult subjects (19/38, 50 %) [8]. Similarly, in a phase II trial, fever was reported as one of the most common adverse events (18.2 %, 6/33) in the dalbavancin group, which was higher than the comparison group treated with vancomycin (5.9 %, 2/34) [9]. In the pooled analysis of DISCOVER1 and DISCOVER 2, non-inferiority trials of dalbavancin for the treatment of acute bacterial SSTIs, fever was reported among 8/652 (1.2 %) patients in the dalbavancin group [10]. A pooled analysis of all phases II and phases III randomized clinical trials has revealed that adverse events associated with dalbavancin typically emerge at a median of 3 days following administration. Once they occur, these events persist for a median duration of 3 days [4]. Further post-marketing studies are needed to estimate the true incidence and pattern of dalbavancin fever.

From experience with other classes such as long-acting injectable antiretrovirals, it is considered a best practice to administer a shorter-acting medication in the same class before starting a long-acting injectable [11]. Our patient had tolerated vancomycin without any adverse reactions, before receiving dalbavancin. Glycopeptides contain a common heptapeptide core structure, which enables them to inhibit cell wall synthesis by binding to the C-terminal D-alanyl-D-alanine of the peptidoglycan chains [12]. Given the structural similarities, cross-reactivity is a concern in patients [12]. However, available data examining the risk of cross-reactivity is scarce. In the very limited data available on cross-reactivity between vancomycin and dalbavancin, no cross-reactivity has been reported to our knowledge [13]. Lack of cross-reactivity has been attributed to a non-IgE-mediated vancomycin reaction as IgE-mediated vancomycin hypersensitivity, which carries the highest risk of cross-reactivity and severe reaction is less common [12, 14]. However, caution should be taken when administrating dalbavancin in the context of a known vancomycin allergy. In such situation a dalbavancin-graded challenge can be attempted Further work is required to define the risk of cross-reactivity and actions to be taken when concern is present, akin to the recently developed and validated PEN-FAST clinical decision rule [15].

There is a lack of guidelines on how to manage dalbavancin adverse events. Given the extended half-life and lack of reversal options, patients should be educated about the side effects and potential of long-duration symptoms. If patients experience adverse events, we recommend close follow-up and symptomatic treatment. When adverse effects have been noted following long-acting injectables from other drug classes such as antipsychotics, treatment ranges from medications to target IgE-mediated and T-cell-mediated mechanisms of action (e.g. epinephrine, antihistamines, and steroids) [16].

Our case highlights the potential for fever as a possible adverse effect and the lack of guidance in the management of dalbavancin adverse events given the long half-life. With increasing practice trends towards more outpatient management of patients through outpatient parenteral antibiotic therapy and oral step-down strategies, dalbavancin is an appealing option. Moreover, the recently completed DOTS study revealed non-inferiority of dalbavancin compared to vancomycin (results presented at late breakers clinical trials session at European Congress of Clinical Microbiology and Infectious Diseases 2024 meeting) for uncomplicated *S. aureus* infection. Hence, use of dalbavancin will continue to increase as it becomes more widely incorporated into routine practice [17]. Given this, further post-marketing study of dalbavancin adverse events is needed with guidance on management options.

Ethical approval

The Emory institutional review board waives the need for review of case reports.

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Author contribution

All authors contributed to initial draft, review and editing of the report.

Consent

Informed consent was obtained from the patient for publication of this case report

Author statement

All authors (MAA, CW, BA, SG, AB) contributed to initial draft, review and editing of the report

CRediT authorship contribution statement

Claire Wan: Writing – review & editing, Writing – original draft, Conceptualization. **Mohamed A. Almahal:** Writing – review & editing, Writing – original draft, Conceptualization. **Ahmed Babiker:** Writing – review & editing, Writing – original draft, Conceptualization. **Sarah Green:** Writing – review & editing, Writing – original draft, Conceptualization. **Benjamin Albrecht:** Writing – review & editing, Writing – original draft, Conceptualization.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Ahmed Babiker reports a relationship with Beckman Coulter Inc that includes: board membership. Ahmed Babiker was supported in part by an Antibacterial Resistance Leadership Group Early Faculty Seedling Award [National Institute of Allergy and Infectious Diseases

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