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Case Report

Oritavancin-Induced Toxic Epidermal Necrolysis (TEN): A Case Report

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Abstract

Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) are severe immune responses to an external stimulus which can lead to significant rates of mortality. Oritavancin is a lipoglycopeptide approved for the treatment of acute bacterial skin and skin structure infections. Oritavancin possesses an extremely long half-life that allows the advantage of a single one-to-three-hour infusion. While prior reports showed few occurrences of SJS/TEN in patients treated with other lipoglycopeptide antibiotics such as dalbavancin, there are no reports for oritavancin. The purpose of this case report is to notify the medical community of an SJS/TEN reaction to oritavancin, of which none have been documented prior to this report. This patient was admitted and treated in the burn intensive care unit of Doctors Hospital of Augusta in October 2023. TEN was diagnosed and treated following a standard protocol and the acute phase of TEN including sloughing of the skin did subside soon after admission. This case report documents the first occurrence of SJS/TEN in an oritavancin patient and allows this condition to be included as a possible adverse drug reaction to this agent.

Keywords: Stevens-Johnson Syndrome; Toxic Epidermal Necrolysis; Oritavancin; Skin Infection; Case Report

Abbreviations: ABSSSI: Acute Bacterial Skin and Skin Structure Infections; SSSI: Skin and Skin Structure Infection. OSH: Outside Hospital; DHOA: Doctors Hospital of Augusta; TEN: Toxic Epidermal Necrolysis.

Introduction

Severe cutaneous adverse reactions are a heterogeneous group of delayed T cell-mediated hypersensitivity reactions, which include Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS) and acute generalized exanthematous pustulosis (reviewed in [1]). SJS and TEN are characterized by extensive erythema, epidermal necrosis, and sloughing of the skin and mucosa [2]. The exact mechanism by which this reaction occurs is unknown but is believed to involve the offending drug agent's inhibition of detoxification pathways leading to an increase in reactive oxygen species (ROS). This rise in ROS is hypothesized to be the trigger of the apoptosis, or cell death that occurs in SJS/TEN [3]. These two conditions can possibly be life-threatening diseases with mortality rates of up to 67% in TEN and 40% in SJS [4]. SJS and TEN are on the same spectrum and differ namely in two regards; affected total body surface area (TBSA) and differentiations in biopsy results with the extent of skin detachment. SJS usually affects less than 10% of TBSA while TEN commonly affects greater than 30% of TBSA. TEN is extremely rare, occurring in around 1.9 patients per million per year, but maintains a mortality rate of approximately 30% in all cases. The stimuli that lead to this condition vary but most often present as medications. Other causes of SJS/TEN may, however, include vaccines, bacterial or viral infections, and even tumors [3]. The distinction between SJS or TEN is not always clear at first

but patient management is similar in response to both conditions. The first steps in this care process include the discontinuation of the offending agent and quick referral to an experienced Burn ICU.

One common class of medications that can lead to SJS/TEN is antimicrobial agents. Certain antimicrobials are notorious for causing this condition with sulfonamides being the most common class comprising 32% of SJS/TEN cases related to antimicrobials [5]. Oritavancin, a lipoglycopeptide like dalbavancin and telavancin was FDA approved in 2014 for the treatment of acute bacterial skin and skin structure infection. Figure-1 shows timeline of the discovery and FDA-approval of glycopeptides. This novel antibiotic possesses an extremely long half-life (245 hours) that allows it to work in the body for over a week [6]. It does not require adjustment for renal or hepatic insufficiency and can be administered in a single one-to-three-hour infusion [7]. There are few occurrences of SJS/TEN in patients treated with lipoglycopeptide antibiotics. For instance, dalbavancin, a lipoglycopeptide antibiotic, has only one reported case of SJS and one case of TEN to date [8]. To the best of our knowledge, there have been no other recorded incidences of SJS/TEN with other lipoglycopeptides and none, prior to the writing of this case study, in patients treated with oritavancin (Figure 1).

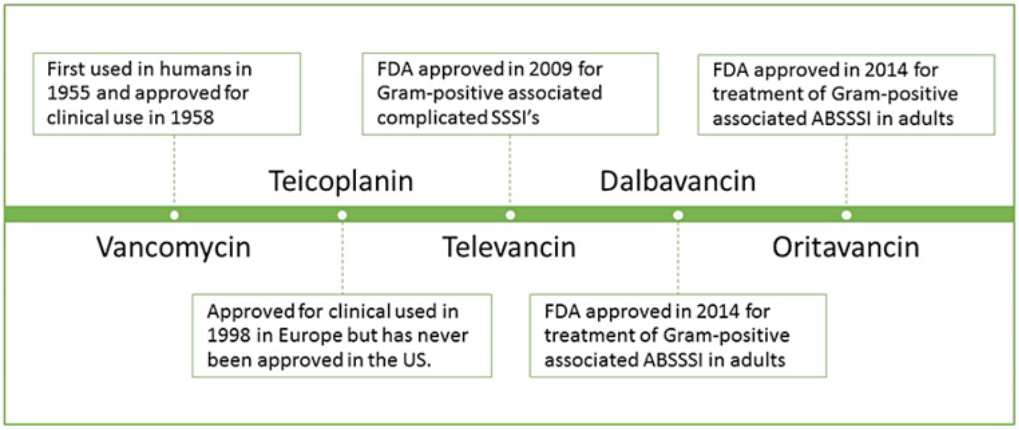

Figure 1: A chart shows the chronology of discovery and use of glycopeptide antibiotics where Vancomycin was the first and Oritavancin is the most recent one to be approved.

Case Presentation

LD is a 54-year-old African American female who received treatment with oritavancin for a refractory chronic wound infection. Her diagnosis shows idiopathic chronic venous hypertension of both lower extremities with ulcer and inflammation. The wounds on the left lower extremity had been present for two years and the right lower extremity wound for six months. Her wounds were treated extensively with oral doxycycline, clindamycin and ciprofloxacin as an outpatient and infusion of vancomycin and meropenem as inpatient along with topical specialty combination of gentamicin-vancomycin-itraconazole all used within the last 3 months. This previous list is not all-inclusive as not all medical records could be obtained from the multiple facilities, but it shows part of an extensive treatment regimen for the patient's chronic wounds. The patient's past medical history was significant for pulmonary embolism, lymphedema, hypertension, congestive heart failure, anxiety, depression, and hypothyroidism. Of note, medication allergies included sulfa antibiotics filed as severe due to rash formation and amlodipine with a similar reaction.

As depicted in Figure 2, the patient was admitted on September 19 to an outside facility and started on vancomycin and cefepime due to an uncontrolled, refractory chronic wound infection. On September 26th, LD received a single infusion of oritavancin over 3 hours as the patient required IV antimicrobials but was not a candidate for discharge with IV access. The patient was scheduled for discharge to a rehabilitation facility; however, the patient had insurance issues and on September 29 was discharged home instead. The patient soon after developed a progressive desquamating rash on October 5th and was re-admitted to the same outside facility with increased weakness, and discomfort, as well as worsening signs and symptoms of possible SJS and TENs. She was referred to JMS Burn Center at Doctors Hospital Augusta for definitive wound care and was placed in the Burn ICU. The patient arrived to our facility on October 8, awake and oxygenating well on room air, but with significant oral sloughing and mild stridor. Upon initial examination, the patient was ill-appearing but alert, although unable to respond and follow commands appropriately. The desquamating rash was assessed and determined to involve the hands, upper abdomen, thighs, mouth and vagina involving approximately 23% of TBSA. Punch biopsies taken from the left chest and left thigh showed findings consistent with TENs.

A fragment of subcutaneous tissue with denuded superficial squamous epithelium and fragments of the epidermis and subcutaneous tissue with chronic inflammation aided in the final diagnosis. The face demonstrated no orbital involvement. The mucosal sloughing led to bleeding, with noticeable dry blood around the mouth. The bilateral upper extremities were then examined and demonstrated Nikolsky sign to lower arms. There was epidermal tissue loss and slough with erythematous wound bed on the back. The anterior torso also demonstrated signs of epidermal tissue loss and denuded skin with a moist, pink erythematous wound bed. The bilateral lower extremities exhibited chronic wounds of large, open areas with exposed muscle for which the patient was receiving original antibiotic treatment. The patient appeared well perfused with only slightly elevated lactate. She was also confirmed to be suffering from metabolic acidosis on admission with a lactic acid of 2.8 mmol/L (Figure 2).

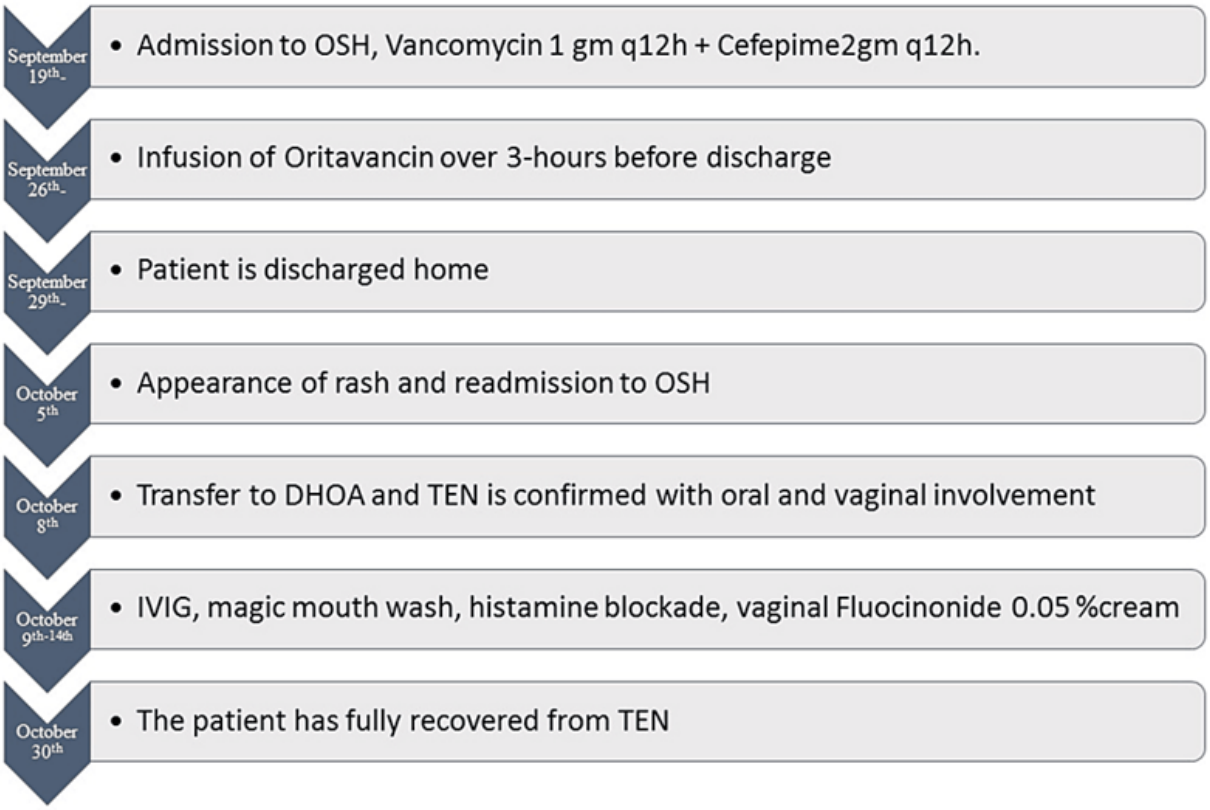

Figure 2: The diagram shows the timeline of the patient's antibiotic administration and development of TEN.

Management and Outcome

The patient was electively intubated and placed on the ventilator to protect the airway. The patient was hypertensive post-intubation and required intravenous anti-hypertensives. A nasogastric tube was later placed for nutritional purposes and enteral access. Intravenous immunoglobulin treatment at a dose of 1gm/kg daily was initiated for a five-day course with the intention to regulate the immune response and inflammation. An acute kidney injury occurred early in her hospitalization course and was treated with an infusion of lactated ringers and sodium bicarbonate was used to treat the patient's metabolic acidosis. Micafungin was started for possible esophageal candidiasis before patient arrival and was continued upon arrival. Zyvox and cefepime were started as empiric coverage until infectious disease could be consulted and proper cultures obtained. Once cultures were received the patient's antimicrobial regimen was changed from cefepime to meropenem to treat Pseudomonas aeruginosa and Achromobact xylo. xylosoxidans. Zyvox was kept to treat Methicillin-resistant Staphylococcus aureus (MRSA). Fexofenadine, famotidine, and as-needed diphenhydramine were initiated for histamine blockade. Fluocinonide 0.05 % cream was administered intravaginally for vaginal involvement and LACRI-LUBE ophthalmic ointment for ocular involvement. For treatment of the patient's chronic bilateral lower extremity wound, necessary debridement procedures

were performed and antibiotics were adjusted as cultures and susceptibilities were obtained. After 3 weeks, the patient had fully recovered from TEN. The patient's initial immune response had subsided soon after admission to Doctors Hospital and no further sloughing was observed. Supportive care was continued until reepithelization occurred. The patient's immune reaction having, for the better part, reached an end, and their other health conditions could be prioritized. The chronic wounds became the primary focus of treatment and antimicrobial therapy was tailored to the cultures obtained.

Discussion

The glycopeptide family of antibiotics has grown and includes the standard glycopeptides (vancomycin, teicoplanin) and lipoglycopeptides (telavancin, oritavancin, dalbavancin). They continue to be utilized for the treatment of resistant Gram-positive infections, in particular MRSA and Enterococcus faecium (reviewed in [9]). Adverse-drug reactions that occur with use of glycopeptide antibiotics include both nonimmune-mediated reactions such as nephrotoxicity and non-immunoglobulin E (IgE) mediated mast cell reactions like red man syndrome [10], as well as immune-mediated reactions such as IgE-mediated hypersensitivity (e.g. anaphylaxis) and T-cell-mediated severe cutaneous adverse reactions [11]. Vancomycin, a widely used glycopeptide, has been reported to cause non-IgE mediated reactions. This antibiotic has been identified as causing up to 40% of DRESS syndrome cases [10,12]. Vancomycin, has been shown also to trigger SJS/TEN and currently has been found responsible for 276 reported cases of this condition [13]. Dalbavancin, a lipoglycopeptide antibiotic, which is closely related to oritavancin, has been reported to cause one case of SJS and one case of TEN to date [8]. Currently, to our knowledge, this is the first report for an incident of TEN with oritavancin.

Cross-reactive immune-mediated reactions between antimicrobials within the same group of antibiotics have previously been reported. However, there is little data on cross-reactivity between glycopeptides and lipoglycopeptides given that a reaction to one of these agents generally halts use of the other agents [14]. It is interesting that the patient was on vancomycin for a week prior to receiving a single dose of oritavancin at the outside hospital. This may present a confounding factor to the oritavancin-induced TEN observation study. There was no definitive way to determine if one caused their immune reaction over the other or if both agents had a part to play. Nevertheless, the patient's records showed prior administration of various antibiotics including vancomycin with no significant immune reaction. Furthermore, the onset of TEN-symptoms started about 10-days post the administration of oritavancin (terminal half-life is 245hr [7]), supporting the notion that oritavancin was likely the trigger for TEN. The symptoms of SJS/TEN are likely to start one to four weeks after exposure to offending agent [3]. Whether lipoglycopeptides may also cause a similar reaction to glycopeptide in patients is a possibility that warrant further studies to provide more data for the medical community to draw conclusions.

The purpose of this report is to provide a first step in understanding the severe immune TEN reactions to oritavancin. Traditionally, treatment in SJS/TENs patients consists of supportive measures including fluid resuscitation, hemodynamic stabilization, wound care, and pain management until the affected skin is re-epithelialized [15]. In this patient case, intubation was elected to protect the airways due to oral involvement. Pain management may consist of opiates and other traditional analgesic agents. Another important area of treatment in these patients is nutritional support. SJS/TENs are hypercatabolic disease states and thus focus should be placed on increasing the patient's anabolic potential. Pharmacotherapy for these patients currently has no proven efficacy but certain agents show promise in decreasing the severity of this condition [3]. For our patient, she received fexofenadine, famotidine, and as needed diphenhydramine for histamine blockade. She also received intravenous immunoglobulin treatment (1 gm/kg/day) for a five-day course to regulate the immune response and inflammation. Fluocinonide 0.05 % cream was administered intravaginally for vaginal involvement. The impact of IVIG on recovery time and mortality has been studied [16,17]. A Meta-analysis showed that IVIG combined with corticosteroid could reduce recovery time for SJS and TEN whereas, its impact on reducing mortality is not significant [16]. The patient's initial immune response had subsided within 3-days after admission to Doctors Hospital and the sloughing was ceased. After 3 weeks, the patient has fully recovered from TEN.

Conclusions

Stevens-Johnson syndrome and toxic epidermal necrolysis (SJS/TEN) are on a spectrum of cutaneous drug reactions characterized by pan-epidermal necrosis with SJS affecting < 10% of body surface area, TEN > 30%. Antimicrobial agents are closely associated with SJS/TEN with sulfonamides causing about one-third of cases. Oritavancin is a lipoglycopeptide approved for the treatment of acute bacterial skin and skin structure infections. Oritavancin possesses an extremely long half-life that allows it to work in the body for over a week and provides the advantage of single one-to-three-hour infusion. While prior reports showed few occurrences of SJS/TEN in patients treated with other lipoglycopeptide antibiotics such as dalbavancin, there are no reports for oritavancin.

Here, we describe the first occurrence of a TEN case to oritavancin that was successfully managed at the burn ICU at Doctors Hospital of Augusta. This serves as the initial step in determining the likelihood of this reaction for other patients

utilizing similar drug therapy in the future. It will take additional cases to gather enough data and confirm the likelihood of oritavancin-induced TEN in hope to aid the medical community in its endeavor to treat patients safely and efficiently.

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