· Case Report ·

Severe drug eruption induced by ozanimod hydrochloride capsules: clinical analysis of a case

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Abstract

Ozanimod is an oral sphingosine-1-phosphate receptor modulator approved for the induction and maintenance of remission in multiple sclerosis and ulcerative colitis. Although generally well tolerated, several reports have described the occurrence of malignancies following ozanimod therapy. We now report a rare case of a severe drug eruption that developed one week after initiation of ozanimod therapy.

Keywords: severe drug eruption, oral sphingosine-1-phosphate receptor modulator, clinical analysis

Introduction

Severe drug eruptions are characterized by extensive skin lesions accompanied by toxic systemic symptoms and visceral involvement. These include exfoliative dermatitis, toxic epidermal necrolysis (TEN), Stevens–Johnson syndrome (SJS), and drug-induced hypersensitivity syndrome [1]. TEN is a life-threatening subtype, characterized by widespread rashes, mucosal involvement, systemic symptoms, and a high risk of severe complications, with a mortality of 1%–5% [2]. Ozanimod is a potent agonist of sphingosine-1-phosphate receptor 1 (S1P1) and receptor 5 (S1P5), which was approved in China in January 2023 for multiple sclerosis (MS). This report describes the first known case of a severe drug eruption following administration of ozanimod.

Case Report

A 55-year-old man presented with a one-week history of diffuse erythema, bullae, epidermal detachment, and painful pruritus. Two weeks earlier, he had started on ozanimod capsules (0.92 mg qd) for MS. One week before presentation, erythema with pruritus appeared on both lower limbs and progressively spread to the whole body, accompanied by worsening pain and pruritus. Bullae developed on the trunk and arms; the bullae contained clear fluid and ruptured easily. Large areas of epidermal detachment appeared on his back. His past history included hypertension for 5 years (controlled with amlodipine) and a cerebral infarction 6 months earlier, with irregular use of medication.

Physical examination revealed stable vital signs. The trunk and extremities, partially coalescing into patches

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and blanching on pressure, were accompanied by a burning sensation. A diffuse erythematous rash involving more than 30% of the total body surface area was observed. Multiple large flaccid bullae were present on the trunk and extremities, associated with marked epidermal necrosis and extensive skin detachment. A positive Nikolsky sign was elicited. Multisite mucosal involvement was also noted, including the oral and genital areas. Based on the extent of epidermal detachment and systemic involvement, the SCORTEN severity score at admission was 3 (Figure 1A and 1B). Laboratory tests, including a complete blood count, transfusion-related tests, lymphocyte subset analysis, Treg cell testing, and cerebrospinal fluid showed no significant abnormalities. Serum potassium was low (3.2 mmol/L). electrocardiogram was normal. Whole-body positron emission tomography/computed tomography on July 24, 2024 showed: multiple low-density lesions in the centrum semiovale, periventricular areas, and basal ganglia bilaterally. Some lesions had a long axis perpendicular to the ventricles and demonstrated poor metabolic activity. Combined with the findings on magnetic resonance imaging, MS was considered possible and follow-up was recommended. Brain magnetic resonance imaging (without contrast) on August 5, 2024 showed: multiple demyelinating lesions in the brain, considered consistent with MS, with a recommendation for clinical correlation The diagnoses were bullous epidermal detachment-type drug eruption, toxic epidermal necrolysis, demyelinating disease of the central nervous system (the primary diagnosis), MS, hypokalemia, chronic ischemic cerebrovascular disease and grade 2 hypertension.

After admission, the patient was treated with intravenous immunoglobulin for neutralization of antibodies and toxins and for immune modulation, along with corticosteroid therapy, neuroprotective treatment, fluid supplementation, antiplatelet therapy, lipid-lowering and plaque-stabilizing agents, blood pressure control, potassium and calcium supplementation, gastric protection, and supportive symptomatic treatment. The skin lesions were mostly dried and healed without new eruptions. The patient improved and was discharged (**Figure 1C and 1D**).

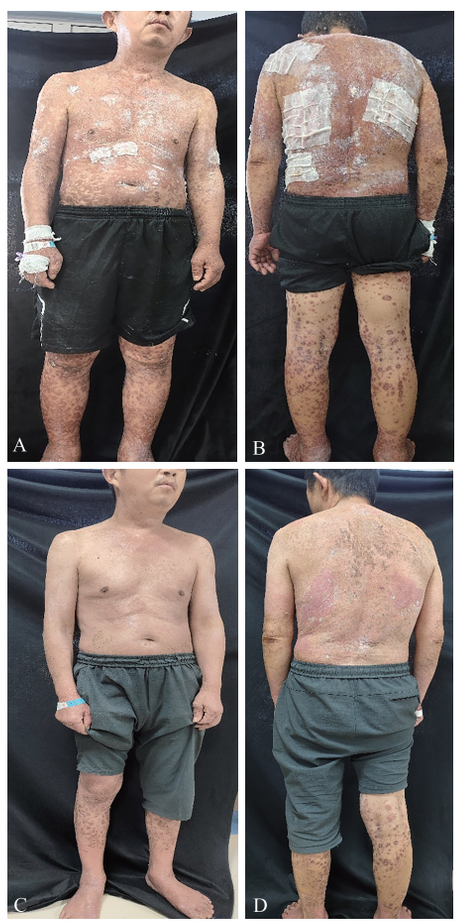

Figure 1. Condition of the skin on the on the patient's front and back upon admission (A, B) and at the time of discharge (C, D).

The patient returned for outpatient follow-up one month later, at which time his skin lesions were continuing to improve, but with dryness and hyperpigmentation.

Discussion

This patient had the following characteristics: a clear medication history (ozanimod) before onset of the

rash; lesions typical of a drug eruption, namely, bullae, epidermal detachment, and bright red erosions on the trunk and limbs; and a good response to corticosteroids and intravenous immunoglobulin. Based on these clinical features, the diagnosis of bullous epidermal-dissolution-type drug eruption could be clearly established. Its classification is toxic epidermal necrolysis. The patient's prognosis was satisfactory after the above-mentioned treatments. Nevertheless, several aspects of this case warrant further discussion and consideration. A review of the relevant local and international literature did not reveal any reports of ozanimod inducing severe drug eruptions. To the best of our knowledge, this case represents the first such reported instance.

Ozanimod was originally developed for the treatment of MS and was approved for ulcerative colitis in May 2021. In clinical studies of the efficacy and safety of ozanimod in patients with MS, the reported incidence of herpesvirus infections was relatively low, ranging from 0.2% to 1.1% [3,4]. The patient had been taking antihypertensive medications for approximately 5 years, whereas ozanimod (0.92 mg once daily) had been administered only within the past 2 weeks for the treatment of tuberous sclerosis. Therefore, antihypertensive medication can essentially be ruled out as a cause of the drug eruption, and ozanimod was the more likely causative agent. However, this study has several limitations, including the absence of ozanimod rechallenge and in vitro allergy testing. Consequently, a definitive causal relationship between ozanimod and the observed drug rash cannot be established and requires further investigation.

This case represents the first reported instance of severe drug eruption associated with ozanimod. Severe drug eruptions can be life-threatening, yet no similar cases have been documented abroad. Possible explanations for the lack of other reports in the literature include the fact that ozanimod was introduced in China only in 2023, resulting in limited exposure time and fewer clinical cases, and the potential genetic or ethnic differences in other countries. Infectious factors are known to play an important role in the pathogenesis of drug eruptions. Luo Xia et al. [5] reported that human herpesvirus-6 (HHV-6) infection, – either primary or reactivated, – is associated with drug-induced hypersensitivity syndrome. Drug eruptions induced by anticonvulsants and allopurinol are closely related to activation of latent HHV-6. A retrospective study demonstrated that patients with allopurinol-induced severe drug eruptions showed HHV-6 DNA positivity in blood, and HHV-6 DNA was also detectable in cerebrospinal fluid. In this case, virus-related testing was not completed, but clinicians should remain vigilant about this potential mechanism. Whether Ozanimod can cause HHV-6 reactivation and be involved in the occurrence of drug eruption requires further research in the future.

As a sphingosine-1-phosphate (S1P) receptor modulator, ozanimod has been linked to cardiovascular adverse events and a potential increase in malignancy risk [6-8]. In a phase III trial evaluating its efficacy and safety in patients with ulcerative colitis (UC), eight individuals developed malignancies–including basal cell carcinoma, colorectal adenocarcinoma, breast cancer, and Kaposi sarcoma (KS) [9] –although no cases of severe drug eruptions were observed. The biological mechanisms potentially underlying these malignancy-related concerns may involve ozanimod's impact on cellular proliferation and migration, processes that could facilitate tumor cell survival Furthermore, its immunosuppressive properties may impair immune surveillance, while the drug-related increase in herpesvirus infections may theoretically predispose patients to herpesvirus-associated malignancies, including KS [8,10]. These findings highlight the need for

vigilance regarding the possible oncogenic risks associated with ozanimod. However, the patient described in this report had only a brief exposure to the medication, and the current evidence remains insufficient to establish a causal association between ozanimod therapy and tumor development. Additionally, this patient exhibited mild but progressively increasing liver enzyme levels. Although nonspecific, this biochemical indicator exception raises concern for early-stage DRESS (Drug Reaction with Eosinophilia and Systemic Symptoms), a hypersensitivity reaction known to manifest with elevated transaminases [11]. The coexistence of hepatic abnormalities and dermatologic manifestations underscores the importance of prompt recognition and comprehensive evaluation to differentiate drug-related hypersensitivity from other potential complications.

Dynamic monitoring of liver function and herpesvirus status is warranted in patients with severe cutaneous adverse reactions to S1P receptor modulators given their potential relevance. Patients prescribed these agents should be informed about the risk of herpesvirus-associated malignancies. Long-term follow-up in the patient described here will focus on these indicators. Whether S1P receptor modulators can also induce viral reactivation leading to drug eruptions remains unclear, and the mechanism by which ozanimod induces drug eruptions requires further investigation.

TEN is a rare but severe reactive disease of the skin and mucous membranes, with an incidence of approximately 1–2 cases per million population per year, and the incidence increases with age. The incidence is higher in patients with HIV/AIDS and in those with systemic lupus erythematosus. More than 80% of TEN cases are drug-induced. Common culprit drugs include sulfonamides, antiepileptic agents (e. g., carbamazepine and phenytoin), non-steroidal anti-inflammatory drugs, and allopurinol. Other possible etiologies include infections (e. g., Mycoplasma pneumoniae, herpes simplex virus, and cytomegalovirus), vaccines, and environmental chemicals. TEN is a T cell–mediated, delayed-type hypersensitivity reaction. Drugs or infections may activate the immune system and induce apoptosis of keratinocytes, leading to epidermal necrosis and detachment. The mortality rate can reach 30%–50%, with sepsis and multiple organ failure being the major causes of death. TEN is a severe form of adverse drug reaction characterized by widespread erythema, large blistering areas of epidermal detachment, and mucosal erosions. Traditionally, these disorders have been considered to be mediated by drug-sensitized $CD8^+$ T cells that secrete cytotoxic mediators. Clinically, patients often experience intense pain, suggesting activation of nociceptors.

However, recent studies by Huang et al. using single-cell sequencing and immunofluorescence staining have shown an increased density of $CGRP^+$ sensory nerves in the lesional skin of patients with TEN [12]. They also found that CGRP can upregulate interleukin-15 and interleukin-18 receptors on $CD8^+$ T cells, thereby promoting the secretion of cytotoxic mediators. This process depends on the cyclic AMP-activated cation channel HCN2. Their study also demonstrated enhanced cytokine–cytokine receptor interactions in circulating $CD8^+$ T cells from patients with SJS/TEN, along with upregulation of the CGRP receptor component RAMP1. Levels of CGRP and the cytokines interleukin -15 and interleukin -18 were also significantly elevated in local blister fluid from skin lesions. This work reveals the critical role of neuro–immune interactions in SJS/TEN and suggests that targeting this neuro–immune circuit may have both anti-inflammatory and analgesic effects [12,13]. These findings provide novel perspectives for the future treatment of SJS/TEN and hold promise for more effective

therapeutic strategies for patients.

Acknowledgments

We thank Liwen Bianji (Edanz) (www.liwenbianji.cn) for editing the English text of a draft of this manuscript.

Ethics approval and consent to participate

This study was performed in accordance with the Declaration of Helsinki. This human study was approved by the Ethics Committee of Affiliated Hospital of Jiujiang University (Jiangxi Province, China)- approval: jjumer-b-2024-12002.

Author contributions

Juan Du and Qiuhe Song contributed equally to this work. Juan Du and Qiuhe Song conceived and designed the study, performed the literature review, and drafted the manuscript. Meijun Wu supervised the project, provided critical revisions, and finalized the manuscript. All authors reviewed and approved the final version of the manuscript.

Conflict of interest

All authors declare no conflicts of interest.

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