

Dupilumab as a treatment for cutaneous immune-related adverse events induced by immune checkpoint inhibitors: A case series and review of the literature

SAGE Open Medical Case Reports
JCMS Case Reports
Volume 11: 1–4
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DOI: 10.1177/2050313X231195462
journals.sagepub.com/home/sco



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Abstract

Immune checkpoint inhibitors have revolutionized cancer treatment. They can induce cutaneous immune-related adverse events. One patient with immune-related eczema and two with immune-related bullous pemphigoid were successfully treated with dupilumab. Guidelines recommend the use of systemic steroids to manage moderate-to-severe cutaneous immune-related adverse events. They could potentially interfere with immunotherapy. There is a need to find alternative treatments that are safe in a cancer setting.

Keywords

Immunotherapy, immune checkpoint inhibitors, bullous pemphigoid, eczema, dupilumab

Date received: 17 April 2023; accepted: 1 June 2023

Introduction

Immune checkpoint inhibitors (ICIs) have revolutionized the management of many cancers. By inhibiting cytotoxic T lymphocyte-associated antigen-4 (CTLA-4), programmed cell death 1 (PD1), or programmed cell death ligand 1 (PD-L1), they act by releasing T cells inhibitory brakes and activate the immune system to attack the tumor cells. Immune system activation is not specific to the tumor and can induce immune-related adverse events (irAEs). Cutaneous irAEs are common, affecting 10%–60% of patients receiving ICIs,¹ and they include pruritus, eczematous eruption, psoriasis, and bullous pemphigoid (BP). Dupilumab is a human monoclonal antibody targeting IL-4 receptor alpha that inhibits the signaling of Th2/Type 2 inflammatory cytokines interleukin-4 (IL-4) and interleukin-13 (IL-13).² Dupilumab is approved for the treatment of moderate-to-severe atopic dermatitis of 6 months and older patients.² Three cases of cutaneous irAEs managed with dupilumab are presented.

Case 1

A 74-year-old man with chronic lymphocytic leukemia (CLL) received cemiplimab for recurrent invasive cutaneous squamous cell carcinoma (SCC) and metastatic melanoma

(Table 1). Cemiplimab, an anti-PD1, is not approved for melanoma, but other anti-PD1 such as pembrolizumab and nivolumab are approved. The patient had two concomitant cancers and cemiplimab was chosen as anti-PD1. After 17 cycles, he developed an acute dermatitis with severe pruritus over his trunk and scalp. He improved with topical steroids and temporary hold of cemiplimab but relapsed with increased severity when immunotherapy was resumed. A skin biopsy showed subacute dermatitis. He was diagnosed with ICI-related eczema with associated pruritus. Cemiplimab was suspended. He was started on dupilumab. After three doses, his pruritus completely resolved, and his dermatitis significantly improved. Cemiplimab was resumed and he maintained eczema and pruritus control, SCC complete response, and metastatic melanoma partial response after 5 months on dupilumab. He has persistently enlarged lymph nodes likely

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Table 1. Patient characteristics, cancer characteristics, immune-related dermatological side effect and treatments.

Patient	Sex	Age (years)	Cancer	Cancer treatment	irAEs	irAE treatment	Dupilumab dosage	Cancer outcome
1	M	74	Recurrent invasive cutaneous SCC and metastatic melanoma	Cemiplimab (PDI inhibitor)	Eczema and pruritus	- Topical steroids - Oral antihistamine	Loading dose 600 mg followed by 300 mg every other week	SCC complete response and metastatic melanoma partial response
2	M	78	Stage IIIC cutaneous melanoma	Adjuvant nivolumab (PDI inhibitor)	BP	- Topical steroids - Oral prednisone	Loading dose 600 mg followed by 300 mg every other week	Remission
3	F	70	Metastatic serous endometrial carcinoma	Pembrolizumab (PDI inhibitor) and Lenvatinib (multi-target tyrosine kinase inhibitor)	BP	- Topical steroids - Doxycycline - Nicotinamide - Oral prednisone - Mycophenolate mofetil	Loading dose 600 mg followed by 300 mg every other week	Death from cancer progression

BP: Bullous pemphigoid; SCC: squamous cell carcinoma. PDI: programmed cell death 1; irAE: immune-related adverse event.

Informed consent to receive dupilumab as an off-label medication for irAEs was obtained from all our patients after a thorough discussion involving their medical oncologist.

from his CLL; however, without biopsy, metastatic melanoma to lymph nodes cannot be ruled out. He has also developed immune-related vitiligo.

Case 2

A 78-year-old man received 1 year of adjuvant nivolumab for stage IIIC cutaneous melanoma. Eight months after he completed nivolumab, he developed BP (Table 1). He initially presented with widespread pruritus and erosions. Biopsies showed eosinophilic spongiosis on hematoxylin and eosin (H&E) staining and linear Immunoglobulin G (IgG) and C3 on direct immunofluorescence. He was treated with clobetasol but continued to be symptomatic and was then managed with prednisone 30 mg daily (~0.4 mg/kg). His course was complicated by steroid-induced diabetes. He was symptomatic when the prednisone was decreased below 15 mg daily. Dupilumab was started as a steroid-sparing agent after 2 months of starting prednisone. He was able to successfully taper off prednisone 2 months later. On dupilumab monotherapy, his pruritus is well controlled, he has no new erosions or bullae, and has no evidence of melanoma recurrence.

Case 3

A 70-year-old woman received pembrolizumab plus lenvatinib in part of a clinical trial for recurrent high-grade serous endometrial carcinoma (Table 1). After 21 cycles, she developed a pruritic “maculopapular” eruption. After 24 cycles, pembrolizumab was discontinued due to clear-fluid bullae development while continuing to receive lenvatinib. Biopsies showed a subepidermal bullae with perivascular lympho-eosinophilic infiltrate on H&E and IgG linear deposits at the

dermoepidermal junction on direct immunofluorescence. She was diagnosed with ICI-induced BP and treated with clobetasol, doxycycline, and nicotinamide with partial improvement. Oral prednisolone 1 mg/kg daily was added, she improved significantly, and prednisone was tapered. However, she experienced cancer progression with brain metastasis and lenvatinib was discontinued. While off cancer treatment, her BP was still active. She was treated with mycophenolate mofetil (MMF) and low-dose prednisone with reasonable control. She experienced further cancer progression with peritoneal metastases and pembrolizumab plus lenvatinib were restarted as post-study treatment. She experienced BP flare despite MMF, low-dose prednisone, and clobetasol. Cancer treatment was held, MMF was discontinued because of lack of efficacy, and high-dose steroids were restarted. Dupilumab was then initiated, she significantly improved, and prednisone was tapered to 10 mg daily over 4 weeks. She was rechallenged with pembrolizumab plus lenvatinib and received two cycles. Her BP remained in remission with dupilumab and low-dose prednisone. However, imaging revealed growing peritoneal, liver, spleen, and lymph node metastases. Pembrolizumab plus lenvatinib were discontinued and she received paclitaxel with a mixed response. She decided to stop all cancer treatments. After 3 months, she died in the palliative care service.

Discussion

ICIs have demonstrated efficacy against several tumors. They are now widely used with both palliative and curative intent for many cancers. Despite the significant benefits of ICIs, the immune system activation is not specific to the tumor and can induce mild to life-threatening irAEs.

Different publications suggest that patients experiencing one or more irAEs have improved overall survival (OS) and progression free survival (PFS).^{3–5} Cutaneous irAEs can occur anytime during or even after immunotherapy and include isolated pruritus, eczema, psoriasis, lichenoid eruption, BP, vitiligo, morbilliform exanthema, and Stevens–Johnson syndrome/toxic epidermal necrolysis.¹

In current guidelines, the mainstay of treatment for moderate-to-severe irAEs are systemic steroids, including for Common Terminology Criteria for Adverse Events (CTCAE) grade 2 to 4 cutaneous irAEs.^{6,7} However, the use of systemic steroids for patients receiving ICIs is controversial with conflicting data.¹ Some studies show that systemic steroids are associated with decreased OS and PFS,^{8–10} especially with high doses.^{11,12} Escalating immunosuppression compromises ICI efficacy even more.¹³ Patients receiving systemic steroids alone had a longer PFS and OS than patients being treated with steroids plus second-line immunosuppressant for grade 3 or higher irAEs. Other studies suggest that there is no difference in OS and PFS between patients receiving immunotherapy plus steroids and patients receiving immunotherapy alone.¹⁴

Dupilumab has been used off-label for pruritus, prurigo nodularis, and BP unrelated to ICIs and there are ongoing clinical trials studying these potential indications. Dupilumab has also been evaluated in 11 patients with ICI-induced BP^{15–18} and in 2 patients with ICI-induced eczema¹⁹ and was successful in all of them. In our case series, we describe the off-label use of dupilumab to manage cutaneous irAEs. Since dupilumab is not an immunosuppressive medication, it may be a safer therapy than systemic steroids both from direct side effects and possibly decreased risk of compromising the anticancer response. Dupilumab is not contraindicated in patients with malignancies.² There is no data supporting that dupilumab may affect the evolution of cancer. There is an ongoing phase Ib/2 trial evaluating the effect of adding dupilumab to PD-L1 inhibitors to treat relapsed/refractory metastatic non-small cell lung cancer.²⁰

There is a need to utilize systemic treatment for cutaneous irAEs that are effective and safe without interfering with ICI response. Further research beyond the mounting case reports, including this one, is required to assess dupilumab's effectiveness and safety in an oncological setting. It is encouraging that research is underway to identify if dupilumab may even be beneficial to increase antitumor responses to immunotherapy.

Acknowledgements

None.

Declaration of conflicting interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: C.F. was a consultant for Sanofi. M.B.S. was a consultant and did trials with Sanofi.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Patient consent

All patients gave consent for the publication of their case.

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