

**CORRESPONDENCE**

# Reply to “New-onset bullous pemphigoid after inactivated Covid-19 vaccine: Synergistic effect of the Covid-19 vaccine and vildagliptin”

To the Editor,

We read with interest the report “New-onset bullous pemphigoid after inactivated Covid-19 vaccine: Synergistic effect of the Covid-19 vaccine and vildagliptin” recently published by Bostan et al. in this journal.<sup>1</sup>

The Authors described the case of a 67-year-old man developing new-onset bullous pemphigoid (BP) 5 weeks after the administration of the first dose of an unspecified inactivated COVID-19 vaccine. Intriguingly, the patient had been on vildagliptin for the last 10 years, due to his diabetes mellitus. The patient was treated with a combination of omalizumab and adequately tapered systemic corticosteroids, achieving only partial disease control.

Recently, we came across three similar patients on dipeptidyl peptidase 4 inhibitors (DPP4-i) presenting with mild-to-moderate BP after vaccination with mRNA COVID-19 vaccines (Table 1). The first was an 85-year-old man on sitagliptin since early 2020 who developed an intensely pruritic cutaneous eruption in November 2021, following the second dose of the Pfizer anti-Severe Acute Respiratory Syndrome CoronaVirus 2 (SARS-CoV-2) vaccine. Itch had appeared immediately after the first dose. Upon physical examination, the rash consisted of tense bullae lacking the characteristic erythematous base of classic BP and excoriated lesions (Figure 1A,B). On histology, eosinophil-rich infiltrates and subepidermal blistering were observed (Figure 1C). Direct immunofluorescence showed linear C3c deposits along the dermal–epidermal junction (DEJ). Indirect immunofluorescence revealed linear IgG positivity along the DEJ, with roof side binding on salt-split skin. On enzyme linked immunosorbent assay (ELISA), autoantibody titers for anti-BP180 and anti-BP230 were 44 and 21 U/ml, respectively.

The other two cases presented similarly, with BP onset occurring between the first and the second dose of anti-SARS-CoV-2 vaccine (Pfizer). Both patients had been taking linagliptin for years before the diagnosis. Although patient n.2 had negative ELISA results and patient n.3 was only weakly positive for BP180, immunoblotting on keratinocyte extracts allowed us to demonstrate frank humoral reactivity against BP180.

DPP4-i discontinuation, topical clobetasol and either oral doxycycline (patient n.1) or prednisone (patient n.2 and n.3) were recommended, reaching partial disease control at 1 month.

Evidence concerning the relationship between DPP4-i and SARS-CoV-2/COVID-19 is conflicting. A recent systematic review of the

literature including nine studies and more than four thousand individual cases demonstrated that DPP4-i are associated with slightly lower mortality in COVID-19 patients.<sup>2</sup> Moreover, DPP4-i may also be beneficial in non-diabetic COVID-19 patients.<sup>3</sup> Although DPP4 is the receptor for the Middle East Respiratory Syndrome-CoronaVirus, SARS-CoV-2 does not appear to bind to DPP4 to a significant degree.<sup>4</sup> Rather, the putative role of DPP4-i in ameliorating the prognosis of COVID-19 patients may be related to their complex immunomodulatory effects.<sup>5</sup>

Several cases of anti-SARS-CoV-2-vaccine-associated BP have been observed.<sup>6</sup> Clinically, two of our patients recalled the non-inflammatory phenotype of gliptin-associated BP originally described by Japanese authors. Indeed, a latency of 1 year since culprit drug initiation would still fall in the range of DPP4-i-associated BP.<sup>7</sup> However, the timing suggests at least a contributing, synergistic role of the vaccine. A dysregulated immune response following anti-SARS-CoV-2 vaccination may target hemidesmosomal components more easily on a DPP4-inhibited background. In addition, DPP-4 is a cell-surface plasminogen receptor capable of converting plasminogen into plasmin, a serine protease that is in turn capable of cleaving BP180 ectodomain.<sup>5</sup> Inhibition of plasmin could provoke an altered processing of BP180 with a possible breakdown in immune tolerance of the antigen. Also, the additive role of mechanical injury secondary to intramuscular inoculation of the vaccine cannot be disregarded.<sup>8,9</sup> Finally, it should be noted that the incidence of DPP4-i/vaccine-associated BP cases is very low when compared with the proportion of vaccinated elderly diabetic individuals on DPP4-i. Thus, an underlying individual predisposition unmasked by coincidental vaccination cannot be ruled out.

## CONFLICT OF INTEREST

The authors declare no conflict of interest.

## AUTHOR CONTRIBUTIONS

All authors have made substantial contribution to the work and have approved the final version of this article. Carlo Alberto Maronese and Giovanni Di Zenzo contributed to study conception and design. Francesca Barei, Alice Monestier, Chiara Moltrasio, and Anna Pira contributed to data analysis. Carlo Alberto Maronese and Giovanni Di Zenzo reviewed the pertaining literature. Carlo Alberto Maronese, Giovanni Di Zenzo, Giovanni Genovese, and Angelo Valerio Marzano edited and approved the final draft.

**TABLE 1** Demographics, clinical, and immunopathological features of reported patients with anti-SARS-CoV-2-vaccine/gliptin-associated BP

Patient n. Sex, age (years)	Anti-SARS-CoV-2 vaccine	Vaccine (1st dose) to BP onset (weeks)	DPP4-I	DIF	ELISA IgG anti-BP180 (U/ml) <sup>a</sup>	ELISA IgG anti-BP230 (U/mL) <sup>a</sup>	Immunoblot on keratinocyte extracts	BPDAI	
								Baseline	At 1 month
n. 1 M, 67	Pfizer	3–4	Vildagliptin	C3c + along the DEJ	44	21	NA	21	8
n. 2 F, 84	Pfizer	4	Linagliptin	NA	11.5	3.6	Positive	18	14
n. 3 M, 86	Pfizer	2	Linagliptin	NA	20.9	0.4	Positive	11.6	NA

Abbreviations: BP, bullous pemphigoid; BPDAI, Bullous Pemphigoid Disease Area Index; DEJ, dermal–epidermal junction; DIF, direct immunofluorescence; ELISA, enzyme linked immunosorbent assay; NA, not available; SARS-CoV-2, Severe Acute Respiratory Syndrome CoronaVirus.

<sup>a</sup>Positive if >20 U/ml.



**FIGURE 1** Clinicopathological features of patient n.1. Tense bulla on a non-erythematous base (A), with concurrent ruptured bullae and erosions (B). Subepidermal detachment and infiltrating eosinophils were demonstrated on histology, consistent with bullous pemphigoid (hematoxylin and eosin, 100×) (C)

#### PATIENT CONSENT STATEMENT

Written informed consent was obtained from the patient for publication of this report and accompanying images.

#### DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study

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