OBSERVATIONS

# Dipeptidyl Peptidase-4 Inhibitors Cause Bullous Pemphigoid in Diabetic Patients: Report of Two Cases

Bullous pemphigoid (BP) is an autoimmune disorder characterized by the production of autoantibodies against two antigens (BPAG1 and 2) and can be induced by drugs (1,2). Recently, the development of BP was reported in diabetic patients treated with dipeptidyl peptidase-4 inhibitors (gliptins) plus metformin (3). However, it remains unknown whether gliptins alone or in combination with metformin are responsible for the induction of BP. We report two diabetic patients who developed BP shortly after addition of vildagliptin to their metformin monotherapy.

A 59-year-old woman and a 67-year-old man, both with type 2 diabetes that had been controlled with metformin for 6 and 3 years, respectively, presented with an 1- and 3-month history of pruritic skin lesions, respectively, that developed 2 months after onset of combined therapy with vildagliptin and metformin. Physical examination revealed a diffuse bullous eruption mostly on an erythematous base. Both patients had no history or evidence of autoimmune, neoplastic, or infectious diseases. In both patients, the results of histological and immunofluorescence investigation of skin biopsy were consistent with the diagnosis of BP. Apart from a slight peripheral eosinophilia, all laboratory investigations were negative. Upon admission, the combined treatment was discontinued in both patients. Patient 1 switched to subcutaneous rapid-acting insulin plus insulin glargine and Patient 2 to metformin plus glimepiride. Upon withdrawal of the gliptin plus metformin combination, there was a significant improvement of eruption, particularly in Patient 2. Patient 1 was treated with 0.5 mg/kg/day methylprednisolone on an 8-week tapering-off scheme, whereas Patient 2 received 200 mg/day doxycycline for a period of 4 weeks. Complete remission was achieved 10 and 8 weeks after discontinuation of vildagliptin plus metformin administration, respectively.

One could argue that in our patients, not vildagliptin but its combination with metformin was involved in the pathogenesis of BP, that the occurrence of the latter was coincidental, or that patients with type 2 diabetes are susceptible to the development of BP. These possibilities cannot be definitely ruled out, however, are very unlikely in view of the following facts: *1*) Literature is devoid of any metformin-induced cases of BP and of evidence for patients with type 2 diabetes being susceptible to developing BP or capable of producing autoantibodies against BP antigens. Furthermore, no interaction between metformin and vildagliptin is known. *2*) There is a striking temporal relationship between vildagliptin addition to long-term metformin monotherapy and the onset of BP. *3*) BP improves upon withdrawal of vildagliptin plus metformin combination. *4*) BP in Patient 2 went into remission despite further metformin administration. Thus, it seems reasonable to suggest that in our patients, the development of BP was due to vildagliptin alone. However, the observations of Skandalis et al. (3) indicate that induction of BP is a side effect most probably shared by all gliptins and not exclusively related to vildagliptin. In view of the wide use of these compounds in the treatment of type 2 diabetes, it is obvious that further studies are now warranted to validate our observations, definitely evaluate the potential of gliptins to cause BP, and to elucidate the corresponding pathogenetic mechanisms.

Efi Pasmatzi, MD[1]
Alexandra Monastirli, MD[1]
John Habeos, MD[2]
Sophia Georgiou, MD[1]
Dionysios Tsambaos, PHD[1]

From the [1]Department of Dermatology, School of Medicine, University of Patras, Patras, Greece; and the [2]Department of Internal Medicine, Division of Endocrinology, School of Medicine, University of Patras, Patras, Greece.

Corresponding author: Efi Pasmatzi, pasmatzi@med.upatras.gr.

DOI: 10.2337/dc11-0804



**Acknowledgments**—No potential conflicts of interest relevant to this article were reported.

E.P. wrote the manuscript. A.M. researched data and helped draft the manuscript. J.H. researched data. S.G. researched data. D.T. reviewed and edited the manuscript. All authors have read and approved the submitted manuscript.

**References**

1. Bastuji-Garin S, Joly P, Picard-Dahan C, et al. Drugs associated with bullous pemphigoid. A case-control study. Arch Dermatol 1996;132:272–276
2. Fellner M. Drug-induced bullous pemphigoid. Clin Dermatol 1993;11:515–520
3. Skandalis K, Spirova M, Gaitanis G, Tsartsarakis A, Bassukas I. Drug-induced bullous pemphigoid in diabetes mellitus patients receiving dipeptidyl peptidase-IV inhibitors plus metformin. J Eur Acad Dermatol Venereol 6 April 2011 [Epub ahead of print]