Comment on "Oral diabetes medications other than dipeptidyl peptidase-4 inhibitors are not associated with bullous pemphigoid: A Finnish nationwide case-control study" and a case report of glucagon-like peptide-1 receptor agonist–induced bullous pemphigoid

To the Editor: We read with interest the recent 2018 article in the *Journal of the American Academy of Dermatology* by Varpuluoma et al titled "Oral Diabetes Medications Other than Dipeptidyl Peptidase 4 Inhibitors Are Not Associated with Bullous Pemphigoid: A Finnish Nationwide Case-Control Study."[1] This population-based investigation presents important findings in the area of drug-induced bullous pemphigoid (BP), particularly given the recent recognition of dipeptidyl peptidase-4 inhibitors as triggers for drug-induced BP in patients with diabetes.[2] However, sample size issues for several medication classes, as well as the emergence of new oral antidiabetic therapies since the study period leave the nature of antidiabetic-associated BP still unresolved. We are concerned that the proclamatory title of the article by Varpuluoma et al, despite substantial residual uncertainty, may predispose readers to prematurely discount the possibility of antidiabetic medication–associated BP in their patients. Further, we present a case report of glucagon-like peptide-1 receptor agonist (GLP-1ra)-induced BP in a patient with diabetes to emphasize the need for ongoing study in this area.

Varpuluoma et al[1] include data from 3397 patients with BP, among whom 17.1% received an oral antidiabetic medication other than insulin between 1997 and 2013. The case against an association between sulfonylurea medications and BP is strong, with 231 patients with BP exposed to medications of that class that were available for comparison with the control population.

However, other medication classes (eg, combination glucose lowering drugs, thiazolidinediones, sodium glucose cotransporter 2 inhibitors, GLP-1ra) were being taken by either no patients or very few patients, and thus, this study is underpowered to reject the likelihood of a meaningful association between these medications and BP. In particular, the study population lacked exposure to a GLP-1ra (n = 1 case), precluding any meaningful conclusions. Conclusions about an association between antidiabetic medications and BP are beyond the scope of this study for all but the sulfonylurea medications, which makes the broadly inclusive and declarative title concerning.

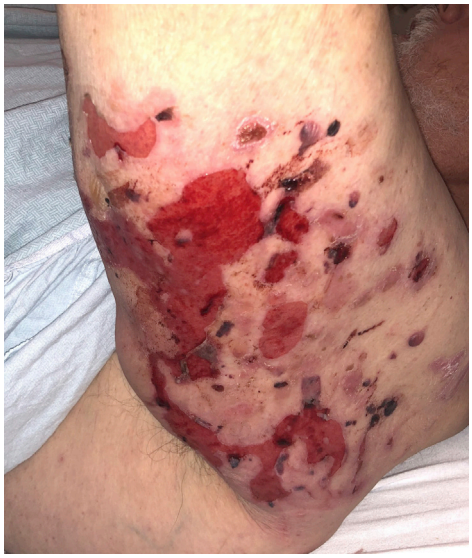

Fig 1. Flaccid bullae and crusted erosions over the left upper extremity of a patient treated with a glucagon-like peptide 1 receptor agonist.

To underscore this point, we herein present the case of a 64-year-old man with non–insulin-dependent diabetes and a history of renal transplantation in 2004 who developed BP 6 weeks after he had begun treatment with the GLP-1ra dulaglutide. The patient presented to our institution after experiencing urticarial lesions, tense bullae, significant pruritus, and erosions over his bilateral upper and lower extremities for several weeks (Fig 1). No other medications were initiated or changed within 6 months of this presentation. A skin biopsy and indirect immunofluorescence confirmed the diagnosis of BP. Dulaglutide was discontinued and the patient was treated with ultrapotent topical corticosteroids. His lesions gradually and fully resolved over the subsequent 3 months.

This case demonstrates the need for ongoing investigation and vigilance in the area of antidiabetic drug–induced BP. The study by Varpuluoma et al[1] presents important evidence that sulfonylureas likely do not induce BP, but it lacks sufficient sample sizes to categorically exclude a potential relationship between BP and other antidiabetic medicines. Despite the article's title, readers should draw no conclusions from the study by Varpuluoma et al about the safety of antidiabetic medications other than sulfonylureas.

Zachary Schwager, MD, Anar Mikailov, MD, and Adam D. Lipworth, MD

From the Division of Dermatology, Lahey Hospital and Medical Center, Burlington, Massachusetts

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Correspondence to: Zachary Schwager, MD, Division of Dermatology, Lahey Hospital and Medical Center, 67 S Bedford Rd, Burlington, MA 01803

E-mail: Zachary.a.schwager@lahey.org

REFERENCES

1. Varpuluoma O, Försti A, Jokelainen J, et al. Oral diabetes medications other than dipeptidyl peptidase-4 inhibitors are not associated with bullous pemphigoid: a Finnish nationwide case control study. *J Am Acad Dermatol*. 2018;79(6):1034-1038.e5.
2. Varpuluoma O, Försti A, Jokelainen J, et al. Vildagliptin significantly increases the risk of bullous pemphigoid: a Finnish nationwide registry study. *J Invest Dermatol*. 2018;138(7):1659-1661.

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