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Gliptin-Associated Bullous Pemphigoid: A Valuable Model of the Mechanism of Breakdown of Immune Tolerance against BP180

Wataru Nishie[1] and Kaisa Tasanen[2]

The study by Plaquevent et al. strongly supports the recent discovery that the use of gliptins is a risk factor for bullous pemphigoid (BP). However, regarding the phenotype of gliptin-associated BP and the necessity of gliptin withdrawal, clinical data remain scarce. We predict that future studies of gliptin-associated BP will offer valuable information concerning autoimmunity against BP180 and may also shed light on the pathology of autoimmune diseases in general.

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Bullous pemphigoid (BP) is a relatively common and well-characterized organ-specific autoimmune disease. Generally seen in elderly patients, BP is caused by a breakdown in immune tolerance of the BP180 protein that is central in epidermal adhesion, but why this happens is still a mystery. Plaquevent et al. (2019) describe the association between dipeptidyl peptidase-4 inhibitor (DPP4i or gliptin) intake and BP onset in a study based on data obtained from the French Study Group on Autoimmune Bullous Skin Diseases and the French reimbursement database. This study confirms that gliptin treatment is a major factor in BP pathogenesis in patients from several ethnic backgrounds, a finding reported in previous studies that were conducted in Finland (Varpuluoma et al., 2018), Switzerland and France (Benzaquen et al., 2018), Israel (Kridin and Bergman, 2018), and Japan (Arai et al., 2018). We believe that gliptin-associated BP represents a useful model for the investigation of the mechanisms behind BP pathogenesis and propose that studies on gliptin-treated patients with diabetes may offer insight into the breakdown of immune tolerance of BP180.

Mechanisms by which gliptins induce the immune system to act against BP180 are currently unknown. Their target molecule, DPP4, also known as CD26, is ubiquitously expressed by various cells, including T lymphocytes (Klemann et al., 2016). It is therefore reasonable to hypothesize that inhibition of CD26 on T cells may affect the immune system. The CD26 protein is known to be involved in the pathophysiology of various autoimmune diseases, including multiple sclerosis and rheumatoid arthritis (Klemann et al., 2016), and it has been suggested that gliptins could decrease the risk of autoimmune diseases but not increase it. However, there are only limited data regarding the expression of CD26 in inflammatory skin diseases such as psoriasis and atopic dermatitis (Klemann et al., 2016), and to best of our knowledge, no study has yet examined the possible involvement of CD26 in BP pathogenesis. A previous study reported that inhibition of DPP4 induces the infiltration of eosinophils into the skin of rats (Forssmann et al., 2008). This is notable because the cutaneous infiltration of eosinophils is a typical histopathologic feature of BP. In addition to various inflammatory cells, DPP4 is also expressed by keratinocytes, and therefore, the effects of DPP4 inhibitors (DPP4is) on the processing, biological activity, or metabolism of BP180 could be involved in the development of gliptin-associated BP. However, gliptins also act on members of the large DPP family other than DPP4, including DPP8 and DPP9. It is thus possible that other substrates may be involved in gliptin-associated BP (Yazbeck et al., 2009). Current data suggest that vildagliptin is the DPP4i most likely to increase the risk for BP (Arai et al., 2018; Benzaquen et al., 2018; Kridin and Bergman, 2018; Varpuluoma et al., 2018), but again, the reason for this is not known. Taken together, there are many interesting questions concerning the pathomechanism that causes the association between gliptins and BP. Future studies must address these questions.

Although this French (Plaquevent et al., 2019) study and a previous Israeli (Kridin and Bergman, 2018) study found no clinical or immunological characteristics that distinguish gliptin-associated BP from "regular" BP, this finding cannot be generalized to all ethnic backgrounds. Recent Japanese studies have reported that, compared with "regular" BP, gliptin-associated BP tends to show a less erythematous, noninflammatory phenotype, with autoantibodies targeting the non-NC16A domains of BP180 (Izumi et al., 2016). Of interest, 86% (18/21) of the noninflammatory gliptin-associated Japanese BP patients had the HLA-DQB1*03:01 haplotype, but this allele was present in only 31% (19/61) of the gliptin-treated, non-BP control individuals (Ujiie et al., 2018). These results suggest that HLA-DQB1*03:01 is strongly associated with drug-related autoimmune disease, and it will be particularly important for future studies to investigate whether this finding extends to other ethnic groups.

Whatever the mechanism behind gliptin-associated BP may be, the long latency time between the beginning of gliptin treatment and the initiation of BP symptoms supports the hypothesis that it is a drug-aggravated condition rather than a drug-induced cutaneous

[1]Department of Dermatology, Hokkaido University Graduate School of Medicine, Sapporo, Japan; and [2]Department of Dermatology, PEDEGO Research Unit, Medical Research Center Oulu, Oulu University Hospital and University of Oulu, Oulu, Finland

Correspondence: Kaisa Tasanen, Department of Dermatology, Medical Research Center Oulu, University of Oulu, Aapistie 5A, FIN-90220 OULU, Finland. E-mail: kaisa.tasanen@oulu.fi

Clinical Implications

- Use of dipeptidyl peptidase-4 inhibitors (gliptins), especially vildagliptin, markedly increases the risk for bullous pemphigoid (BP).
- It is currently unclear whether gliptin-associated BP has specific immunological or phenotypical properties that are distinct from those of BP in individuals who have not received gliptins.
- Although the effect of cessation of gliptin treatment on the clinical outcome of BP is not known at the moment, it may be prudent to replace gliptins with another diabetes medication.

reaction. Therefore, gliptin-associated BP may persist after gliptin cessation. Once a definite diagnosis of BP has been made in a patient who is receiving gliptin therapy, it is important for the dermatologist to decide whether to recommend that the gliptin should be withdrawn or replaced. In contrast to the Plaquevent et al. (2019) study, a recent study from Israel (Kridin and Bergman, 2018) found that discontinuation of gliptins improved clinical outcomes. However, limited sizes of study populations and variation in the treatment of BP patients limits the conclusions that may be drawn from current studies. Because this issue remains unclear, a safe option at the moment is to replace gliptins with another diabetes medication. Combinations of gliptins with metformin are also associated with increased risk of BP, but no such risk has been proven with metformin alone (Kridin and Bergman, 2018; Varpuluoma et al., 2018). This implies that when BP is diagnosed in patients receiving both a gliptin and metformin, the metformin could be safely continued while the gliptin is withdrawn.

During recent years, more epidemiological data have become available regarding factors associated with the onset of BP. Now it is time for research projects that will examine predisposing factors, comorbidities, and disease processes at the level of autoantigen modification and inflammatory pathways to understand the complex immunopathogenesis of BP. For example, a great deal of valuable information on autoimmunity against BP180, and on triggers of autoimmunity in general, could be obtained were it possible to follow BP patients from the preclinical through to the blistering stages of disease. Moreover, characterization of gliptin-associated BP may be an important character in a story that leads to further revelations in other autoimmune diseases.

CONFLICT OF INTEREST

The authors state no conflict of interest.

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Large-Giant Congenital Melanocytic Nevi: Moving Beyond *NRAS* Mutations

Mitchell S. Stark[1]

Large-giant congenital melanocytic nevi have been well characterized clinically, yet questions remain about the heterogenous phenotypes observed. Martins da Silva et al. (2018) highlight the genotypic diversity between "classic" and "spilus-like" congenital melanocytic nevi by analyzing multiple biopsy sites and matching satellite nevi. This study provides evidence for alternative modes of development beyond the well-established *NRAS* mutation paradigm.

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[1]*Dermatology Research Centre, The University of Queensland, The University of Queensland Diamantina Institute, Brisbane, Queensland, Australia*

Correspondence: Mitchell S. Stark, Dermatology Research Centre, The University of Queensland, UQ Diamantina Institute, Level 5, Translational Research Institute, 37 Kent Street, Woolloongabba, Brisbane, QLD 4102, Australia. E-mail: m.stark@uq.edu.au