Rilzabrutinib-induced transition from pemphigus vulgaris to pemphigus foliaceous: a case report and literature review

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Abstract

The discovery of the role of Bruton's Tyrosine Kinase (BTK) in inflammation and autoimmunity has recently led to the development of BTK inhibitors for the treatment of autoimmune diseases, including pemphigus vulgaris. We herein present the case of a patient affected by pemphigus vulgaris, refractory to conventional immunosuppressive therapies and to multiple courses of rituximab, who was treated with rilzabrutinib and achieved disease control, but whose immunological profile switched from pemphigus vulgaris to pemphigus foliaceus after drug discontinuation. Furthermore, we reviewed the literature to better characterize the phenotypic transitions from pemphigus vulgaris to pemphigus foliaceus reported so far. The factors underlying this transition are largely unknown, although it has been postulated that immunosuppressive therapies may be more effective against anti-desmoglein 3 (DSG3) antibodies compared to anti-desmoglein 1 (DSG1). However, further studies are needed to clearly define the effect of rilzabrutinib (and immunosuppressive therapies in general) on anti-DSG1 and anti-DSG3 antibodies.

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Consent for publication: the patient gave his written consent to use his personal data for the publication of this case report and any accompanying images.

Availability of data and materials: all relevant data pertaining to this case report are included within the manuscript. Additional information or data is available upon reasonable request to the corresponding author.

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Introduction

Bruton's Tyrosine Kinase (BTK) is a non-receptor intracellular kinase that is expressed mainly in B cells and myeloid cells. It contributes to both physiological and malignant proliferation of B lymphocytes and several cellular pathways in myeloid cells involved in inflammation, phagocytosis, and antimicrobial defenses.[1] The role of BTK in autoimmunity has led to the development of selective BTK inhibitors that have shown their efficacy and safety in several conditions, including pemphigus vulgaris (PV). The efficacy of BTK inhibitors in PV was first reported in a patient suffering from paraneoplastic pemphigus induced by chronic lymphocytic leukemia: in this patient, ibrutinib, a first-generation BTK inhibitor, led to the achievement of disease control of both chronic lymphocytic leukemia and pemphigus skin lesions.[2] Recently, second- and third-generation BTK inhibitors have been developed. Among these, rilzabrutinib, which covalently reversibly binds BTK, showed encouraging results in a phase 2 open-label cohort study in human patients with PV,[3] and a phase 3 trial of rilzabrutinib *vs.* placebo (PEGASUS; NCT03762265) has recently ended. Nonetheless, the effects of this drug on the immunological profile of PV patients are currently unknown.

Pemphigus foliaceus (PF) and PV, the two most common subtypes of pemphigus, have distinct clinical, histological, and immunological features. PV differs from PF because it frequently involves mucous membranes and is characterized by suprabasal involvement; PF, instead, does not display mucosal involvement and is characterized by subcorneal acantholysis.[4] Antibodies against desmoglein 3 (DSG3) are found in mucosal-dominant PV, while antibodies against desmoglein 1 (DSG1) and DSG3 are found in mucocutaneous PV. Patients with PF, on the other hand, only show antibodies against DSG1.[5] Transitioning from PV to PF is a rare occurrence, and the transition from PF to PV is even rarer, with only a few cases reported.[6-8] The mechanism underlying this phenotypic transition is currently unknown.

We herein present the case of a patient affected by PV refrac-

tory to conventional immunosuppressive therapies and to multiple courses of rituximab, who was treated with rilzabrutinib and achieved disease control, but whose immunological profile switched from PV to PF after drug discontinuation. Furthermore, we review the literature to better characterize the phenotypic transitions from PV to PF reported so far.

Case Report

A 64-year-old man was admitted to the Dermatology Unit of Padova University Hospital in December 2015 with a 6-month history of painful erosions involving the oral cavity (buccal and palatine mucosa, gingivae, and ventral surface of the tongue) and isolated erosions on the presternal area. The patient complained mainly of difficulty in swallowing, pharyngolaryngeal pain, and hoarseness; video laryngoscopy was performed, showing supraglottic inflammation with mucosal erosions covering the oropharynx and larynx.

Histological examination showed suprabasal acantholysis, and direct immunofluorescence demonstrated IgG and C3 deposits on the keratinocyte cell surfaces in all layers of the epidermis. Enzyme-linked immunosorbent assay (ELISA) identified serum antibodies against DSG1 and DSG3 (17.45 U/mL and 162.17 U/mL, respectively). The diagnosis of PV was made, and the patient started therapy with oral prednisone (75 mg/day, then gradually tapered), oral minocycline (100 mg/day), and oral nicotinamide (500 mg/day), resulting in progressive healing with re-epithelialization of erosions within 5 months. In 2018, the patient experienced a relapse in oral mucosal pemphigus; since azathioprine therapy was contraindicated due to abnormal liver enzymes, he started treatment with oral prednisone (50 mg/day, then gradually tapered) and ultra-low-dose rituximab (a single intravenous infusion of 200 mg), with gradual improvement of skin lesions. An ultra-low-dose rituximab regimen was employed based on evidence that lower doses (<1500 mg per cycle) are not inferior to higher doses (≥2000 mg per cycle) in achieving remission, disease control, or reducing relapse rates,[9] and on a pilot study suggesting that a single 200 mg infusion can be effective in achieving disease control while minimizing potential side effects.[10] In 2019 a new relapse of PV occurred, and the patient was then prescribed prednisone (50 mg/day, then gradually tapered) and dapsone (50 mg/day). Due to inadequate control of the disease, he received a new infusion of rituximab 200 mg, resulting in a partial resolution of skin lesions.

In May 2020, the patient presented with painful erosions involving the oral cavity, wide erosions on his back and chest, and crusted erosions on his scalp; he was then enrolled in phase 3 randomized, parallel-group, double-blind, placebo-controlled trial (PEGASUS; NCT03762265) of oral rilzabrutinib (PRN1008) *vs.* placebo in moderate to severe PV or PF. During the blinded treatment period, he received PRN1008/placebo orally twice daily for 37 weeks, along with oral corticosteroids; he then received rilzabrutinib 400 mg twice daily until the study completion date in December 2021 (week 80), achieving complete remission of the disease. In February 2022, ELISA testing revealed a serological profile compatible with PF: anti-DSG1 30.32 U/mL and anti-DSG3 11.05 U/mL. At that time, skin lesions were limited to isolated crusted erosions on the patient's back. The clinical and serological findings suggested a transition from PV to PF. We then decided to study the trend of anti-DSG1/anti-DSG3 levels from December 2015 to February 2022 (Figure 1). We observed that before rilzabrutinib therapy and during the blinded treatment period of the trial, the levels of anti-DSG1 and anti-DSG3 antibodies were both positive. During the open-label extension period of the trial, rilzabrutinib treatment led to a progressive decrease in anti-DSG1 and anti-DSG3 levels. However, after discontinuation of the drug, anti-DSG1 antibodies started to rise again, while anti-DSG3 antibodies remained below the cut-off level, suggesting a transition to PF.

Discussion

We report the case of a patient affected by PV refractory to conventional therapies who was enrolled in rilzabrutinib trial (PEGASUS; NCT03762265) and achieved disease control but whose clinical and immunological phenotype switched from PV to PF after drug discontinuation. We conducted a review of the literature and the characteristics of patients who exhibited a clinical and immunological transition from PV to PF (*Supplementary Table 1*).[6,11-22] The case reports and case series presented to date did not focus on previous therapies or ongoing treatments during the transition. Nonetheless, C. Lévy-Sitbon and colleagues described the case of a patient whose phenotype changed from PV to PF two years after completing a course of four infusions of rituximab.[19] In this article, the authors postulated a greater efficacy of immunosuppressive treatments on the production of anti-DSG3 rather than anti-DSG1 antibodies. However, it is not possible to determine if the immunosuppressive therapies currently available for the treatment of PV are more effective on the production of anti-DSG3 antibodies than anti-DSG1 antibodies. Rituximab treatment does not appear to be associated with this switch. As a matter of fact, to date, only two cases of clinical and immunological switch from PV to PF have been described in patients previously treated with rituximab.[19,20]

The phenotypic transition more often occurs during a disease relapse, after immunosuppressive therapy discontinuation or reduction. The factors underlying this transition during a relapse are still largely unknown. The epitope-spreading mechanism has been proposed to explain the transition from PF to PV; in PF only anti-DSG1 antibodies are present, but during the course of the disease, DSG3 might be released from injured tissue and exposed to the immune system, leading to the production of anti-DSG3 anti-

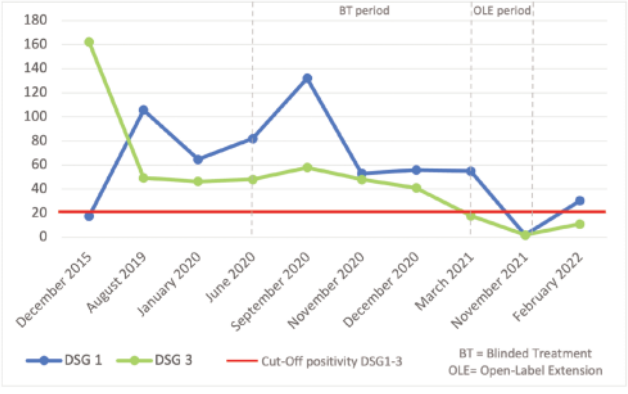

Figure 1. Graphical representation of the trend over time, and in relation to trial phases, of antibodies against DSG1 and DSG3. It shows how, after the PRN1008 administration, the anti-DSG1 and 3 levels decreased to 0, while after discontinuation of PRN1008, the anti-DSG1 antibodies increased again; instead, the anti-DSG3 antibodies stayed below the cut-off level of positivity.

bodies.[23] However, this mechanism cannot explain the switch from PV to PF, which is characterized by a progressive reduction of the titer of anti-DSG3 antibodies.

Conclusions

To the best of our knowledge, no cases of clinical and/or serological transition from PV to PF in patients treated with rilzabrutinib (PRN1008) have been reported so far. Furthermore, there is a paucity of data regarding the trend of anti-DSG1 and anti-DSG3 antibody titers during the treatment with this innovative molecule. The inversion of the ratio between anti-DSG3 and anti-DSG1 antibodies, observed in our patient, may have been induced by rilzabrutinib or may be due to the largely unknown factors underlying the transition from PV to PF in patients treated with immunosuppressants. Further studies are needed to better define rilzabrutinib's effect on anti-DSG1 and anti-DSG3 antibody titers.

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Online Supplementary Material
Supplementary Table 1. Cases of pemphigus with transition from PV to PF.