



## Dermatology Reports

<https://www.pagepress.org/journals/index.php/dr/index>

eISSN 2036-7406



**Publisher's Disclaimer.** E-publishing ahead of print is increasingly important for the rapid dissemination of science. **Dermatology Reports** is, therefore, E-publishing PDF files of an early version of manuscripts that undergone a regular peer review and have been accepted for publication, but have not been through the copyediting, typesetting, pagination and proofreading processes, which may lead to differences between this version and the final one.

The final version of the manuscript will then appear on a regular issue of the journal.

E-publishing of this PDF file has been approved by the authors.

Please cite this article as: Ciolfi C, Tartaglia J, Pampaloni F, et al. **Rilzabrutinib-induced transition from pemphigus vulgaris to pemphigus foliaceus: case report and review of the literature.** *Dermatol Rep* 2024 [Epub Ahead of Print] doi: 10.4081/dr.2024.10010

 © the Author(s), 2024

Licensee [PAGEPress](https://www.pagepress.org/), Italy

Submitted - Accepted

Note: The publisher is not responsible for the content or functionality of any supporting information supplied by the authors. Any queries should be directed to the corresponding author for the article.

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article or claim that may be made by its manufacturer is not guaranteed or endorsed by the publisher.

## **Rilzabrutinib-induced transition from *pemphigus vulgaris* to *pemphigus foliaceus*: case report and review of the literature**

Christian Ciolfi,<sup>1\*</sup> Jacopo Tartaglia,<sup>1\*</sup> Francesca Pampaloni,<sup>1</sup> Laura Fagotto,<sup>1</sup> Andrea Sechi,<sup>2</sup> Mauro Alaibac<sup>1</sup>

<sup>1</sup>Dermatology Unit, Department of Medicine (DIMED), University of Padova; <sup>2</sup>Dermatology Unit, San Bortolo Hospital, Vicenza, Italy

\*equally contributed to this work

**Correspondence:** Francesca Pampaloni, Dermatology Unit, Department of Medicine (DIMED), University of Padova, 4 Gallucci Street, Padova 35134, Italy.

Tel.: + 39.3487554070

E-mail: [francesca.pampaloni@gmail.com](mailto:francesca.pampaloni@gmail.com)

**Key words:** *pemphigus vulgaris*; *pemphigus foliaceus*; Bruton's tyrosine kinase; rilzabrutinib; desmoglein.

**Conflict of interest:** the authors declare no conflict of interest.

**Fundings:** none.

**Contributions:** all authors contributed to designing and conducting the work, drafting and revising the manuscript and approved the final version for submission.

**Ethics approval and consent to participate:** the need for Ethics approval was waived for this case report.

**Patient consent for publication:** the patient provided both written and verbal consent to participate in this study.

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

**Acknowledgements:** we extend our heartfelt appreciation to all those who contributed to this research. Our gratitude goes to all the staff at the Dermatology Clinic for their valuable support throughout the study. We are also thankful to the participant for their willing participation, which made this research possible.

## **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 review the literature in order 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 antibodies compared to anti-desmoglein 1. However, further studies are needed to better define the effect of rilzabrutinib (and immunosuppressive therapies in general) on anti-desmoglein 1 and anti-desmoglein 3 antibodies.

## **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 to several cellular pathways in myeloid cells involved in inflammation, phagocytosis and antimicrobial defenses.<sup>1</sup>

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 disease control achievement of both chronic lymphocytic leukemia and *pemphigus* skin lesions.<sup>2</sup>

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<sup>3</sup> 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 more 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.<sup>4</sup> Antibodies against desmoglein 3 (DSG 3) are found in mucosal-dominant PV, while antibodies against desmoglein 1 (DSG 1) and DSG 3 are found in mucocutaneous PV.<sup>5</sup> Patients with PF, on the other hand, only show antibodies against DSG 1.<sup>5</sup> Transitioning from PV to PF is a rare occurrence, and the transition from PF to PV is even rarer, with only few cases reported.<sup>6-8</sup> The mechanism underlying this phenotypic transition is currently unknown.

We herein present the case of a patient affected by PV 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 PV to PF after drug discontinuation. Furthermore, we review the literature in order 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 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 DSG 1 and DSG 3: 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-epithelization 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 therapy 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 ( $\geq 2000$  mg per cycle) in achieving remission, disease control, or reducing relapse rates,<sup>9</sup> and on a pilot study suggesting that a single 200 mg infusion can be effective in achieving disease control while minimizing potential side effects.<sup>10</sup> 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 raise 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) achieving disease control, but whose clinical and immunological phenotype switched from PV to PF after drug discontinuation. We performed a review of the literature and the characteristics of patients who showed a clinical and immunological transition from PV to PF, summarized in Supplementary materials, Table 1.<sup>6,11-22</sup> The case reports and case series presented to date did not focus on previous therapies or ongoing treatments at the time of 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.<sup>19</sup> 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 certainly state if the immunosuppressive therapies currently available for the treatment of PV are more effective in the production of anti-DSG3 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.<sup>19,20</sup>

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 antibodies.<sup>23</sup> However, this mechanism can not explain the switch from PV to PF, which is characterized by a progressive reduction of the titer of anti-DSG3 antibodies.

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 antibodies titer 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 effect on anti-DSG1 and anti-DSG3 antibodies titer.

## References

1. Patsatsi A, Murrell DF. Bruton Tyrosine Kinase Inhibition and Its Role as an Emerging Treatment in Pemphigus. *Front Med (Lausanne)* 2021;8:708071.
2. Lee A, Sandhu S, Imlay-Gillespie L, et al. Successful use of Bruton's kinase inhibitor, ibrutinib, to control paraneoplastic pemphigus in a patient with paraneoplastic autoimmune multiorgan syndrome and chronic lymphocytic leukaemia. *Australas J Dermatol* 2017;58:e240-2.
3. Murrell DF, Patsatsi A, Stavropoulos P, et al. Proof of concept for the clinical effects of oral rilzabrutinib, the first Bruton tyrosine kinase inhibitor for pemphigus vulgaris: the phase II BELIEVE study\*. *Br J Dermatol* 2021;185:745-55.
4. Amagai M, Bologna JL, Schaffer JV, Cerroni L. *Dermatology*. 4th ed. New York: Elsevier; 2018. Pemphigus; pp. 494–509.

5. Amagai M, Tsunoda K, Zillikens D, et al. The clinical phenotype of pemphigus is defined by the anti-desmoglein autoantibody profile. *J Am Acad Dermatol* 1999;40:167-70.
6. Komai A, Amagai M, Ishii K, et al. The clinical transition between pemphigus foliaceus and pemphigus vulgaris correlates well with the changes in autoantibody profile assessed by an enzyme-linked immunosorbent assay. *Br J Dermatol* 2001;144:1177-82.
7. Ishii K, Amagai M, Ohata Y, et al. Development of pemphigus vulgaris in a patient with pemphigus foliaceus: Antidesmoglein antibody profile shift confirmed by enzyme-linked immunosorbent assay. *J Am Acad Dermatol* 2000;42:859-61.
8. Awazawa R, Yamamoto Y, Gushi M, et al. Case of pemphigus foliaceus that shifted into pemphigus vulgaris after adrenal tumor resection. *J Dermatol* 2007;34:549-55.
9. Wang HH, Liu CW, Li YC, et al. Efficacy of rituximab for pemphigus: a systematic review and meta-analysis of different regimens. *Acta Derm Venereol* 2015;95:928-32.
10. Russo I, Miotto S, Saponeri A, et al. Ultra-low dose rituximab for refractory pemphigus vulgaris: a pilot study. *Expert Opin Biol Ther* 2020;20:673-8.
11. Iwatsuki K, Takigawa M, Hashimoto T, et al. Can pemphigus vulgaris become pemphigus foliaceus? *J Am Acad Dermatol* 1991;25:797-800.
12. Kawana S. Changes in Clinical Features, Histologic Findings, and Antigen Profiles With Development of Pemphigus Foliaceus From Pemphigus Vulgaris. *Arch Dermatol* 1994;130:1534.
13. Chang SN, Kim SC, Lee IJ, et al. Transition from pemphigus vulgaris to pemphigus foliaceus. *Br J Dermatol*. 1997;137:303-5.
14. Kimoto M, Ohyama M, Hata Y, et al. A Case of Pemphigus foliaceus Which Occurred after Five Years of Remission from Pemphigus vulgaris. *Dermatology* 2001;203:174-6.
15. Harman KE, Gratian MJ, Shirlaw PJ, et al. The transition of pemphigus vulgaris into pemphigus foliaceus: a reflection of changing desmoglein 1 and 3 autoantibody levels in pemphigus vulgaris. *Br J Dermatol* 2002;146:684-7.
16. Toth GG, Pas HH, Jonkman MF. Transition of pemphigus vulgaris into pemphigus foliaceus confirmed by antidesmoglein ELISA profile. *Int J Dermatol* 2002;41:525-7.
17. Tsuji Y, Kawashima T, Yokota K, et al. Clinical and Serological Transition From Pemphigus Vulgaris to Pemphigus Foliaceus Demonstrated by Desmoglein ELISA System. *Arch Dermatol* 2002;138.
18. Ng PPL, Thng STG. Three Cases of Transition from Pemphigus vulgaris to Pemphigus foliaceus Confirmed by Desmoglein ELISA. *Dermatology* 2005;210:319-21.
19. Lévy-Sitbon C, Reguiaï Z, Durlach A, et al. Transition phénotypique d'un pemphigus vulgaire en pemphigus superficiel. *Ann Dermatol Vénéréologie* 2013;140:788-92.
20. España A, Koga H, Suárez-Fernández R, et al. Antibodies to the amino-terminal domain of desmoglein 1 are retained during transition from pemphigus vulgaris to pemphigus foliaceus. *Eur J Dermatol* 2014;24:174-9.

21. Ito T, Moriuchi R, Kikuchi K, et al. Rapid transition from pemphigus vulgaris to pemphigus foliaceus. *J Eur Acad Dermatol Venereol* 2016;30:455-7.
22. Mohammadrezaee M, Etesami I, Mahmoudi H, et al. Transition between pemphigus vulgaris and pemphigus foliaceus: a 10-year follow-up study. *JDDG J Dtsch Dermatol Ges* 2020;18:1302-4.
23. Pigozzi B, Peserico A, Schiesari L, Alaibac M. Pemphigus foliaceus evolving into pemphigus vulgaris: a probable example of ?intermolecular epitope spreading? confirmed by enzyme-linked immunosorbent assay study. *J Eur Acad Dermatol Venereol* 2008;22:242-4.

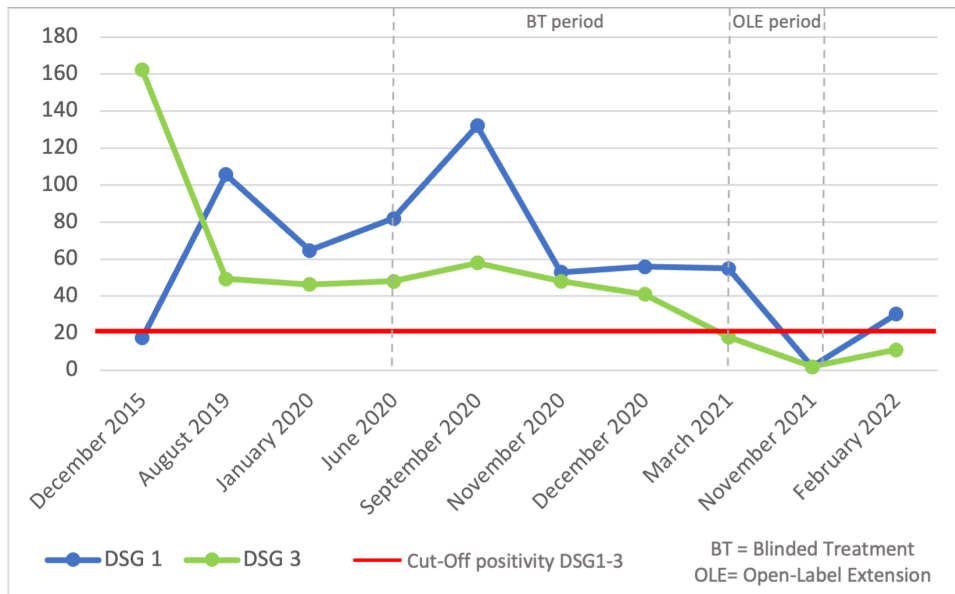


Figure 1. Graphical representation of the trend over time, and in relation to trial phases, of antibodies against DSG 1 and DSG 3. It shows how, after the PRN1008 administration the anti-DSG 1 and 3 levels decreased to 0, while after discontinuation of PRN1008 the anti-DSG 1 antibodies increased again,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

### Online supplementary materials

Table 1. Cases of pemphigus with transition from PV to PF. Legend: F, Female, M, Male, IVIg, Intravenous Immunoglobulins, N/A, not available, DSG 1, desmoglein 1, PV, pemphigus vulgaris, PF, pemphigus foliaceus.