

## Persistent B Lymphocyte Depletion After an Ultralow Dose of Rituximab for Pemphigus Vulgaris

Lazzarotto A, Ferranti M, Meneguzzo A, Sacco G, Alaibac M  
*Dermatology Unit, University of Padua, Padua, Italy*

J Invest Allergol Clin Immunol 2018; Vol. 28(5): 347-348  
doi: 10.18176/jiaci.0283

Key words: Rituximab. Pemphigus. Autoimmunity. Skin. B cells.

Palabras clave: Rituximab. Pénfigo. Autoinmunidad. Piel. Células B.

Pemphigus vulgaris is an autoimmune bullous disease affecting the skin and mucosa. It is caused by autoantibodies targeting the adhesion molecules desmoglein 1 and desmoglein 3, which, respectively, mediate adhesion between keratinocytes in skin and mucosa, resulting in the formation of blisters and erosions. Early recognition and treatment are crucial for remission of this disorder. Treatment for severe pemphigus traditionally includes long-term corticosteroids and immunosuppressants [1]. Rituximab, a chimeric monoclonal antibody against the CD20 antigen of B lymphocytes, was recently introduced and has proven to be effective in resistant and life-threatening pemphigus [2]. Protocols for administration of rituximab are determined for use in non-Hodgkin lymphoma (375 mg/m<sup>2</sup> once a week, with duration depending on the type of lymphoma) and for rheumatoid arthritis (2 doses of 1000 mg given 2 weeks apart) [3]. A lower dose of rituximab (500 mg at 2 weeks interval) can be used in pemphigus [4-6].

A 67-year-old woman was referred to our dermatology department for recent onset of erosive lesions of the oral cavity. The patient complained of severe difficulty swallowing, forcing her to feed almost exclusively with a liquid diet. The skin was not involved, showing only signs of previously active lesions. She denied trauma and application of topical drugs on the areas involved. Her medical history did not reveal any association with other immune-mediated diseases. Evaluation of circulating anti-DSG1, anti-DSG3, and anti-BP180 antibodies revealed a high anti-DSG3 autoantibody titer (192.13 U/mL, normal value <7 U/mL), which is consistent with a diagnosis of pemphigus vulgaris. Treatment was initially started with intravenous methylprednisolone 80 mg/d for 2 weeks, which was thereafter slowly tapered to 40 mg/d over 2 weeks, with complete remission. The patient was then treated with oral prednisone 50 mg/d for 1 month and 25 mg/d for a further month. At this time, the disease relapsed, with oral involvement only, and azathioprine 100 mg/d was combined with prednisone 25 mg/d for 3 months. The oral lesions did not resolve. Consequently, we decided to administer rituximab [7] in a 2-dose regimen (2 weeks apart) of 500 mg per dose. Prior to infusion of rituximab, the patient was premedicated with intravenous acetaminophen 1000 mg, chlorphenamine 10 mg, and methylprednisolone 20 mg diluted in 100 mL of normal saline. Rituximab 500 mg was then diluted in 500 mL of

normal saline and infused at 50 mL/h for the first 30 minutes and then at incremental rates of 50 mL/h every 30 minutes, up to 400 mL/h. However, after 120 minutes, the patient began to complain of chest tightness, the infusion had to be interrupted, and the dose of rituximab was reduced to about 250 mg. Seven days after the administration of 250 mg of rituximab CD19, the B-lymphocyte percentage (pre-B and mature B lymphocytes) was 0%. During the following months, the patient improved, with almost complete remission, and is now receiving low-dose maintenance corticosteroid therapy. Blood tests at 3 months and 6 months after the infusion of 250 mg of rituximab showed a stable 0% rate for CD19<sup>+</sup> B lymphocytes.

The optimal dosage of rituximab for treatment of pemphigus has not been clearly defined. The initially used regimen was that of the lymphoma protocol (375 mg/m<sup>2</sup>) for 4 weeks; thereafter, the protocol used in patients with rheumatoid arthritis (2 infusions of 1000 mg given 2 weeks apart) or a low-dose regimen (500 mg at a 2-week interval) was preferred because of its better safety profile [8]. The clinical improvement and the persistently suppressed CD19 B-lymphocyte count over 6 months of follow-up suggest the potential efficacy of this reduced-dose protocol (single 250-mg dose), which was arrived at purely by chance.

Further studies, especially longitudinal and controlled studies, are needed to confirm both short- and long-term efficacy and the possible better safety profile of this regimen, compared with usual protocols for administration of rituximab in patients with pemphigus vulgaris, especially severe forms resistant to traditional immunosuppressants [9]. In this regard, a recent study [10] demonstrated how a single, minimal dose of rituximab (1 mg/m<sup>2</sup>) effectively depleted CD20<sup>+</sup> cells in healthy volunteers, suggesting that ultralow rituximab regimens could be a plausible approach for the treatment of autoimmune skin conditions.

### Funding

The authors declare that no funding was received for the present study.

### Conflicts of Interest

The authors declare that they have no conflicts of interest.

### References

- Pollmann R, Schmidt T, Eming R, Hertl M. Pemphigus: a Comprehensive Review on Pathogenesis, Clinical Presentation and Novel Therapeutic Approaches. *Clin Rev Allergy Immunol*. 2018;54:1-25.
- Hebert V, Joly P. Rituximab in pemphigus. *Immunotherapy*. 2018;10:27-37.
- Murrell D, Sprecher E. Rituximab and short-course prednisone as the new gold standard for new-onset pemphigus vulgaris and pemphigus foliaceus. *Br J Dermatol*. 2017;177:1143-4.
- Chadha A, Khopkar U, Nitya M, Lahori V. Follow-up data of rituximab as adjuvant therapy in pemphigus. *Indian J Dermatol*. 2017;62:671-3.
- Gupta J, Raval R, Shah A, Solanki R, Patel D, Shah K, et al.

- Low-dose rituximab as an adjuvant therapy in pemphigus. *Indian J Dermatol Venereol Leprol.* 2017;83:317-25.
6. Hertl M, Jedlickova H, Karpatis S, Marinovic B, Uzun S, Yayli S, et al. Pemphigus. S2 Guideline for diagnosis and treatment - guided by the European Dermatology Forum (EDF) in cooperation with the European Academy of Dermatology and Venereology (EADV). *J Eur Acad Dermatol Venereol.* 2014;29:405-14.
  7. Sanchez J, Ingen-Housz-Oro S, Chosidow O, Antonicelli F, Bernard P. Rituximab as Single Long-term Maintenance Therapy in Patients With Difficult-to-Treat Pemphigus. *JAMA Dermatology.* 2018;154:363-5.
  8. Wang H, Liu C, Li Y, Huang Y. Efficacy of Rituximab for Pemphigus: A Systematic Review and Meta-analysis of Different Regimens. *Acta Dermatol Venereol.* 2015;95:928-32.
  9. Kanwar A, Vinay K, Sawatkar G, Dogra S, Minz R, Shear N, et al. Clinical and immunological outcomes of high- and low-dose rituximab treatments in patients with pemphigus: a randomized, comparative, observer-blinded study. *Br J Dermatol.* 2014;170:1341-9.
  10. Schoergenhofer C, Schwameis M, Firbas C, Bartko J, Derhaschnig U, Mader RM, et al. Single, very low rituximab doses in healthy volunteers – a pilot and a randomized trial: implications for dosing and biosimilarity testing. *Scient Rep.* 2018;8:124-5.

■ *Manuscript received March 1, 2018; accepted for publication June 12, 2018.*

**Mauro Alaibac**

Unit of Dermatology  
University of Padua  
Via Gallucci 4  
35128 Padova, Italy  
E-mail: mauro.alaibac@unipd.it