Use of rituximab in the treatment of pemphigus vulgaris in a juvenile patient

Hanna Róża Cisoń, Rafał Białynicki-Birula, Wojciech Baran

Department of Dermatology, Venereology and Allergology, Medical University of Wroclaw, Wroclaw, Poland

Dermatol Rev/Przegl Dermatol 2023, 110, 694–697
DOI: https://doi.org/10.5114/dr.2023.135677

CORRESPONDING AUTHOR:
Hanna Róża Cisoń
Department of Dermatology,
Venereology and Allergology
Medical University of Wroclaw
Wroclaw, Poland
e-mail:
hanna.cison@student.umw.edu.pl

ABSTRACT

Introduction: Pemphigus vulgaris is a chronic autoimmune blistering disorder characterised by the production of autoantibodies against desmogleins, resulting in intraepithelial blister formation. Despite advancements in treatment options, some patients experience disease progression and an inadequate response to conventional therapies. Rituximab, a monoclonal chimeric antibody targeting CD20 on B-cells, has shown promise as an alternative therapeutic option.

Case report: In this case report, we present the management of a 14-year-old child with pemphigus vulgaris who exhibited disease progression despite conventional treatment modalities. The patient was administered rituximab therapy, resulting in significant clinical improvement and disease control.

Conclusions: The utilisation of rituximab as an adjunct or alternative therapy in refractory pemphigus cases offers a valuable treatment option. Further studies and long-term follow-up are necessary to determine the optimal dosing regimen and evaluate the safety and efficacy of rituximab in paediatric pemphigus patients.

Key words: pemphigus, drug therapy, complications, rituximab, administration and dosage, adverse effects.

INTRODUCTION

Pemphigus is a chronic autoimmune disorder classified into two main variants: pemphigus vulgaris (PV) and pemphigus foliaceus (PF). PV is the more common subtype, accounting for 75–92% of all pemphigus cases [1]. Pemphigus vulgaris is characterised clinically by the presence of painful blisters and erosions on the skin and mucous membranes, as well as the presence of autoantibodies against desmoglein 3 and/or desmoglein 1. It most commonly affects individuals between the ages of 30 and 60. The frequency of pemphigus cases in the paediatric population is not determined, but it is estimated to account for 1.4% to 2.9% of all pemphigus cases [2]. The literature on treatment of PV in juveniles is limited and based on case reports [3]. Rituximab (RTX), a monoclonal chimeric antibody that selectively binds to CD20 antigen on B-cells, has emerged as a potentially effective therapeutic option for pemphigus. Since 2017, it has been considered a promising first-line treatment for pemphigus and was granted approval by the U.S. Food and Drug Administration in June 2018 for the management of moderate to severe pemphigus vulgaris in adult patients [4].

CASE REPORT

A 14-year-old child with erythematous, blistering, and erosive lesions was admitted to the Department of Dermatology in Wroclaw in July 2021 (fig. 1). Based on the patient's story, the initial manifestation

of skin lesions occurred in February 2021, and at the beginning only small papules appeared on the labial mucosa. Over time, the lesions progressed, leading to the development of extensive erosions. Subsequently, the caregivers also noted the presence of blisters on the trunk, neck, and intraoral regions. Despite the negative of the DIF test, pemphigus vulgaris was diagnosed due to the clinical presentation of the skin lesions and the presence of circulating pemphigus antibodies (anti-desmoglein 1: 37,77 RU/ml, $n < 20$; anti-desmoglein 3: 110 RU/ml, $n < 20$, ELISA test Euroimmun) (table 1). DIF was not repeated due to significantly elevated levels of circulating anti-desmoglein 1 and anti-desmoglein 3 antibodies. The child also reported swallowing difficulties associated with an escalation of erosions within the oral cavity, as well as impaired ambulation due to the presence of blisters on the plantar surface of the foot. Mycophenolate mofetil therapy was initiated at a dose of 1000 mg q.d. along with systemic glucocorticosteroids (methylprednisolone pulse therapy 250 mg/day i.v. for 3 days (6 pulses) followed by prednisone 30 mg (1 mg per kg of body weight) q.d. and consolidation of the disease was achieved. After 6 weeks, prednisone was discontinued due to complete remission in another outpatient department. Following the cessation of steroid treatment, the patient experienced a recurrence of isolated oral ulcers and the appearance of blisters on both hands. During the clinical visit in September 2021, given the reappearance of cutaneous lesions, the decision was made to reintroduce prednisone therapy at a daily dose of 20 mg, followed by a systematic tapering regimen. Mycophenolate mofetil was continued at a dose of 1000 mg q.d. However, high levels of anti-desmoglein 3 antibodies persisted (August 2022: 115 RU/ml, December 2022: 123 RU/ml) despite treatment. In December 2022, the patient reported the appearance of the new mucosal erosions on the labia majora, which led to the decision of initiating rituximab therapy (RTX). After premedication with 125 mg of methylprednisolone i.v. and 1 mg of clemastine orally, RTX was administered using a flow rate controller over

Figure 1. Blisters on the dorsal aspect of the left foot of a 14-year-old patient

5 hours. During infusion, minor fluctuations in blood pressure were observed, with readings ranging from 127/80 to 94/37 mm Hg. Moreover, the patient also reported nausea and sore throat, but the infusion was continued. The symptoms subsided within the first 2 hours after administration. Two weeks later in accordance with guidelines on the management of pemphigus vulgaris and foliaceus, the second infusion of RTX was administered. Minor complications during drug administration, as outlined in the Summary of Product Characteristics (SmPC), subsided 2 hours after administration. Following the administration of a RTX infusion, it is recommended to sustain therapeutic intervention with a monthly decreasing prednisone dosage. In the initial month post-infusion, the patient adhered to a prednisone regimen of 40 mg once daily (1 mg/kg). Subsequently, during the second month, the dosage was reduced to 30 mg once daily (0.75 mg/kg), followed by 20 mg once daily (0.5 mg/kg) in the third month. In the fourth month, the prescribed dosage was further reduced to 12 mg once daily (0.3 mg/kg), and in the fifth month,

Table 1. Date and level of circulating anti-desmoglein 1 (Anti-Dsg 1) and anti-desmoglein 3 (Anti-Dsg 3) antibodies

Date of ELISA test	Dates of RTX infusions	Anti-Dsg 1 [RU/ml] (normal range: < 2 RU/ml)	Anti-Dsg 3 [RU/ml] (normal range: < 2 RU/ml)
September 2021		37.77	110.96
April 2022		23.47	28.57
August 2022		17.42	115.84
December 2022		10.56	123.6
January 2023		12.72	83.26
	January 19, 2023 February 2, 2023		
April 2023		< 2	62.50

a maintenance dose of 8 mg once daily (0.2 mg/kg) was implemented. Six months post-infusion, in accordance with recommendations, the prednisone dosage was planned to be reduced to 4 mg once daily (0.1 mg/kg). During the routine disease assessment in April 2023, the patient remained asymptomatic, with no reported complaints. Furthermore, clinical examination revealed healthy skin and mucosal surfaces. Notably, the levels of circulating pemphigus antibodies were reduced, as evidenced by the antidesmoglein 3 antibody level of 62.5 RU/ml (reference range: < 20) (table 1).

DISCUSSION

Corticosteroids have been the cornerstone of pemphigus therapy and have significantly reduced mortality rates from this disease. However, high doses of corticosteroids have been associated with serious adverse effects. To reduce the side effects of long-term high-dose steroid therapy, the dexamethasone-cyclophosphamide protocol was introduced in 1984 [5]. In the following years, several adjuvant immunosuppressive drugs, including azathioprine, mycophenolate mofetil, have been used in combination with corticosteroids or as monotherapy, leading to improved outcomes. However, even with these treatments, many patients fail to achieve complete remission or experience adverse events [6]. RTX can eliminate memory B cells, which play a critical role in the pathogenesis of pemphigus, by supporting the formation of short-lived plasma cells that secrete pathogenic autoantibodies. Importantly, rituximab spares long-lived plasma cells, which are involved in maintaining immune memory and providing longterm protection against infections [7]. The production of autoantibodies in pemphigus is thought to result from a disruption in B cell tolerance, leading to the emergence of autoreactive clones that escape central or peripheral deletion mechanisms. Rituximab-mediated depletion of these clones can restore immune homeostasis and alleviate the clinical manifestations of pemphigus [8]. Kong *et al.* [9] treated the first adolescent patient with RTX in 2005, a 17-year-old girl, who had previously failed to respond to other treatments for childhood PV, with a successful outcome without any observed adverse events. Fuertes *et al.* [10] presented a case study of the youngest reported patient with chronic pemphigus vulgaris (CPV) in the literature, an 18-month-old boy, who was monitored for 16 years. The patient underwent several immunosuppressive therapies with varying efficacy until achieving complete remission with RTX. Bilgic-Temel *et al.* [11] reported 5 paediatric patients with pemphigus vulgaris (PV) who were treated with RTX. A favourable clinical response to the treatment was observed in all patients. During the final follow-up visit, 3 patients achieved complete remission without the need for additional therapy, while the remaining 2 patients achieved partial remission. Notably, no adverse events were observed throughout the course of treatment. Kanwar *et al.* [12] treated a 9-year-old child with severe pemphigus vulgaris with rituximab. During the second infusion, the child experienced angioedema, but the infusion was continued at a slower rate without any additional complications. After a follow-up period of 46 weeks, the child achieved complete remission and was no longer receiving treatment. Also in our case, the infusion was continued. Vinay *et al.* [3] reported 10 patients between the ages of 9 to 17 years treated with rituximab therapy, and followed up for a median period of 16 months. Seven patients achieved complete remission without the use of other therapies in an average period of 21 weeks. One patient achieved complete remission on immunosuppressant therapy, one had control of disease activity, and one had partial remission on immunosuppressant therapy. Six patients experienced a relapse or flare within an average period of 13 months. Two patients underwent a second infusion of RTX and had a good clinical response. The most common adverse events were infusion reactions, and no long-term complications were reported. Currently, RTX is considered a first-line therapy for pemphigus [6, 13, 14]. There are few reports in the literature on the use of this therapy in children. During the administration of this drug, minor adverse effects can occur (nausea, sore throat, blood pressure fluctuations, and muscle weakness and pain in the right upper limb that lasts for a few days), which are listed in the Summary of Product Characteristics (SmPC). Although infusion-related side effects may occur during the administration of RTX, it is essential to ensure a continuous infusion of the medication. The precise factors determining the efficacy of RTX treatment remain unknown; however, it is postulated that its impact on memory cells contributes to its therapeutic effects. The extended reduction and delayed restoration of memory B cells post-RTX therapy could potentially stem from the sequestration of immature B cell progenitors within the bone marrow, likely influenced by the robust myelosuppressive effects exerted by concurrent immunosuppressive treatments [15]. To optimise outcomes, it is recommended to administer RTX for a period of up to 6 months following the diagnosis of pemphigus. Furthermore, it is noteworthy that RTX infusion holds particular significance for patients who do not achieve consolidation with conventional medications [13, 14]. Nonetheless, recurrent relapses necessitating repetitive infusions are prevalent. B-cell activating factor (BAFF) are common a critical role in B cell survival, class switch recom-

bination, the selection of autoreactive B cells, and the persistence of long-lived plasma cells. The findings propose a plausible association between the activation of autoreactive B cells at the onset of pemphigus and heightened BAFF serum levels. Furthermore, the diminished expression of BAFF-R subsequent to RTX treatment may potentially contribute to the postponed generation of memory B cells, consequently leading to an extended phase of subdued pemphigus activity following rituximab therapy [16]. We revealed the decrease in antibody levels after 4 months of RTX administration from 83 to 62 RU/ml, and after 6–7 months we expect a decrease in antibody production.

CONCLUSIONS

RTX stands as a frontline therapy for pemphigus, albeit with limited literature regarding its efficacy and safety in children. While minor adverse effects, in line with the Summary of Product Characteristics, may occur during administration, careful monitoring is essential, especially considering potential infusion-related side effects. Despite uncertainties regarding the precise mechanisms underlying its efficacy, RTX's impact on memory cells is postulated to contribute to its therapeutic effects. Further research, particularly focusing on paediatric populations and elucidating its mechanism of action, is warranted to optimise treatment outcomes and minimise adverse effects in pemphigus management.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

References

1. **Hertl M., Eming R., Veldman C.:** T cell control in autoimmune bullous skin disorders. J Clin Invest 2006, 116, 1159-1166.
2. **Yazganoğlu K.D., Baykal C., Küçükoğlu R.:** Childhood pemphigus vulgaris: five cases in 16 years. J Dermatol 2006, 33, 846-849.
3. **Vinay K., Kanwar A.J., Sawatkar G.U., Dogra S., Ishii N., Hashimoto T.:** Successful use of rituximab in the treatment of childhood and juvenile pemphigus. J Am Acad Dermatol 2014, 71, 669-675.
4. **Genentech Press Releases. [(accessed on 7 June 2018)]. Available online:** https://www.gene.com/media/press-releases/14727/2018-06-07/fda-approves-genentechs-rituxan-rituxima
5. **Kanwar A.J., De D.:** Pemphigus in India. Indian J Dermatol Venereol Leprol 2011, 77, 439-449.
6. **Joly P., Horvath B., Patsatsi A., Uzun S., Bech R., Beissert S., et al.:** Updated S2K guidelines on the management of pemphigus vulgaris and foliaceus initiated by the European Academy of Dermatology and Venereology (EADV). J Eur Acad Dermatol Venereol 2020, 34, 1900-1913.
7. **Musette P., Bouaziz J.D.:** B cell modulation strategies in autoimmune diseases: new concepts. Front Immunol 2018, 9, 622.
8. **Hammers C.M., Chen J., Lin C., Kacir S., Siegel D.L., Payne A.S., et al.:** Persistence of anti-desmoglein 3 IgG(+) B-cell clones in pemphigus patients over years. J Invest Dermatol 2015, 135, 742-749.
9. **Kong H.H., Prose N.S., Ware R.E., Hall R.P. 3rd.:** Successful treatment of refractory childhood pemphgus vulgaris with anti--CD20 monoclonal antibody (rituximab). Pediatr Dermatol 2005, 22, 461-464.
10. **Fuertes I., Guilabert A., Mascaró J.M. Jr, Iranzo P.:** Rituximab in childhood pemphigus vulgaris: a long-term follow-up case and review of the literature. Dermatology 2010, 221, 13-16.
11. **Bilgic-Temel A., Özgen Z., Harman M., Kapıcıoğlu Y., Uzun S.:** Rituximab therapy in pediatric pemphigus patients: a retrospective analysis of five Turkish patients and review of the literature. Pediatr Dermatol 2019, 36, 646-650.
12. **Kanwar A.J., Tsuruta D., Vinay K., Koga H., Ishii N., Dainichi T., et al.:** Efficacy and safety of rituximab treatment in Indian pemphigus patients. J Eur Acad Dermatol Venereol 2013, 27, e17-e23.
13. **Joly P., Maho-Vaillant M., Prost-Squarcioni C., Hebert V., Houivet E., Calbo S., et al.:** First-line rituximab combined with short-term prednisone versus prednisone alone for the treatment of pemphigus (Ritux 3): a prospective, multicentre, parallel--group, open-label randomised trial. Lancet 2017, 389, 2031-2040.
14. **Popescu I.A., Statescu L., Vata D., Porumb-Andrese E., Patrascu A.I., Grajdeanu I.A., et al.:** Pemphigus vulgaris – approach and management. Exp Ther Med 2019, 18, 5056-5060.
15. **Boch K., Langan E.A., Schmidt E., Zillikens D., Ludwig R.J., Bieber K., et al.:** Sustained CD19+CD27+ memory B cell depletion after rituximab treatment in patients with pemphigus vulgaris. Acta Derm Venereol 2022, 102, adv00679.
16. **Hébert V., Maho-Vaillant M., Golinski M.L., Petit M., Riou G., Boyer O., et al.:** Modifications of the BAFF/BAFF-receptor axis in patients with pemphigus treated with rituximab versus standard corticosteroid regimen. Front Immunol 2021, 12, 666022.

Received: 31.08.2023
Accepted: 13.02.2024

How to cite this article
Cisoń H.R., Białynicki-Birula R., Baran W.: Use of rituximab in the treatment of pemphigus vulgaris in a juvenile patient. Dermatol Rev/Przegl Dermatol 2023, 110, 694–697. DOI: https://doi.org/10.5114/dr.2023.135677.