Pemphigus vulgaris successfully treated with ocrelizumab following rituximab allergy

Gabrielle Benesh, BS, Tyler M. Andriano, BS, and Steven R. Cohen, MD, MPH
Bronx, New York

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INTRODUCTION

Pemphigus vulgaris (PV) is a rare autoimmune blistering disorder primarily treated with immunosuppressive agents. Rituximab, a chimeric anti-CD20 monoclonal antibody, is widely used as first-line therapy for PV.[1] Anti-CD20 agents, associated biosimilars, and other B-cell depleting agents have also been reported to effectively treat PV.[2,3] Ocrelizumab, a humanized anti-CD20 monoclonal antibody, has not been studied in PV. We describe a case of refractory PV successfully treated with ocrelizumab.

Abbreviations used:

IV: intravenously
PV: pemphigus vulgaris

CASE REPORT

A 53-year-old woman presented in May 2016 with a 5-year history of extensive erosions involving the oral mucosa, face, trunk, abdomen, and extremities. Soft, brown crusts covered most erosions. In 2011, a skin biopsy revealed suprabasilar epidermal acantholysis, and, in 2016, indirect immunofluorescence using monkey esophagus substrate detected intercellular immunoglobulin G deposits (1:80). Since prior trials of methylprednisolone (20 mg daily), azathioprine (150 mg daily), and intravenous immunoglobulin G (180 mg monthly) had not controlled blistering, alternative regimens, including prednisone, dapsone, methotrexate, and rituximab, were initiated (Table I).

While the initial 3-hour infusion of rituximab (1,000 mg; premedicated with methylprednisolone, 100 mg intravenously [IV]; diphenhydramine, 25 mg IV) was well tolerated; the second infusion, 2 weeks later, was terminated because of flushing, generalized pruritus, and urticaria. Subsequent blistering was mild on a regimen of prednisone, dapsone, azathioprine, and methotrexate. Approximately 14 months later, worsening blisters prompted another trial of rituximab. Despite premedication (methylprednisolone, 125 mg IV; diphenhydramine, 50 mg IV; acetaminophen, 650 mg orally), anaphylaxis developed. The patient continued a regimen of prednisone, dapsone, and methotrexate (Table I). Thirteen months later, an attempted 16-step rituximab desensitization protocol was abandoned because of profound and intractable flushing and pruritus. Although attempting to optimize oral therapy using prednisone and dapsone, while substituting methotrexate with cyclophosphamide (Table I), exuberant truncal blistering persisted (Fig 1, *A*). A search for alternative anti-CD20 therapies led to compassionate use of ocrelizumab (Ocrevus), a second-generation, humanized, anti-CD20 monoclonal antibody (Genentech, Inc).

The first of a 2-part ocrelizumab loading dose (300 mg IV) (premedicated with methylprednisolone [100 mg IV], diphenhydramine [50 mg IV], acetaminophen [650 mg orally]) was interrupted by nausea after 100 mg; however, the second loading dose 2 weeks later (300 mg IV) was well tolerated. Marked initial reduction of disease activity within 6 weeks led to another trial substitution of cyclophosphamide with methotrexate. However, since the latter caused debilitating fatigue, and the efficacy appeared similar for both drugs, methotrexate was discontinued, and cyclophosphamide resumed. A remission was sustained for 5 months until recurrent widespread blistering prompted a second premedicated 2-part

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Correspondence to: Steven R. Cohen, MD, MPH, 111 East 210th St, Bronx, NY 10467. E-mail: steven.cohen@einsteinmed.org.
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Table I. Timeline of infusion therapy with concomitant medications

	Dates 6/2016-10/2020	Infusion (mg IV)	Premedications dose (mg), (route of administration)	Prednisone[†] (mg/day)	Dapsone (mg/day)	Cyclophosphamide (mg/day)	Methotrexate (mg/week)
Rituximab							
Loading	Month 0 (Day 0; Day 15)	1000	methylprednisolone 100 (IV); diphenhydramine 25 (IV)	100-40	25	-	10
Relapse	Month 14 (Once)	1000	methylprednisolone 125 (IV); diphenhydramine 50 (IV); acetaminophen 650 (PO)	40-20	75	-	15
Desensitization*	Month 27 (Once)	1000	methylprednisolone 50 (IV); diphenhydramine 50 (IV); montelukast 10 (PO); aspirin 325 (PO); famotidine 20 (IV)	20	75	-	15
Interval treatment regimen	7/2018-3/2019	-	-	50-20	75	150	-
Ocrelizumab							
Loading	Month 0 (Day 0; Day 15)	300; 300	methylprednisolone 125 (IV); diphenhydramine 50 (IV); acetaminophen 650 (PO)	20	75	150	-
	Month 6 (Day 0; Day 15)	300; 300	methylprednisolone 125 (IV); diphenhydramine 50 (IV); acetaminophen 650 (PO)	10	75	-	15
Maintenance	Month 12 (Once)	600	methylprednisolone 125 (IV); diphenhydramine 50 (IV); acetaminophen 650 (PO)	10	75	150	-
	Month 18 (Once)	600	methylprednisolone 125 (IV); diphenhydramine 50 (IV); acetaminophen 650 (PO)	10	75	150	-
	Month 24 (Once)	600	methylprednisolone 125 (IV); diphenhydramine 50 (IV); acetaminophen 650 (PO)	10	75	150	-

IV, Intravenously; *PO*, orally.
*Physician supervised desensitization protocol under direct observation; increasing doses of rituximab were given in 16 steps over 9 hours duration.
[†]Prednisone tapered relative to flares; maintenance dose achieved.

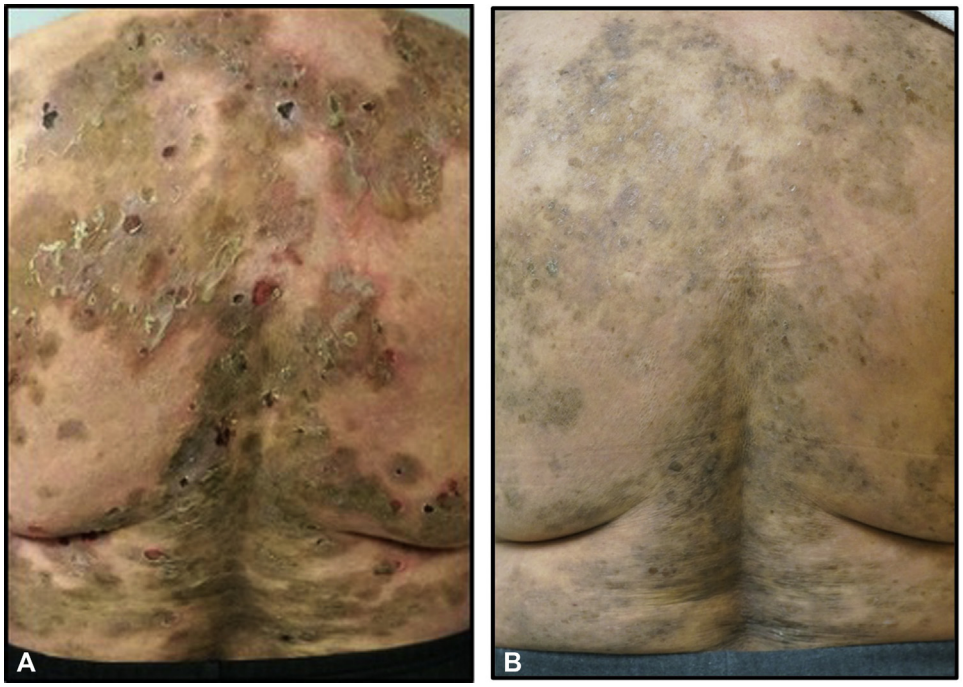

Fig 1. Clinical photographs of pemphigus vulgaris before and after ocrelizumab therapy. **A**, (Month 0) Posterior trunk shows exuberant blistering and flaccid bullae, multiple crusted erosions intermixed with erythematous-to-violaceous plaques and postinflammatory pigment alteration. **B**, (Month 24) After 3 maintenance cycles of ocrelizumab only postinflammatory pigment alteration remains.

loading dose of ocrelizumab at month 6. Subsequently, a durable and near-complete remission has been maintained for more than 2 years, employing maintenance premedicated ocrelizumab (600 mg IV every 6 months as single-dose infusions) in conjunction with prednisone, 10 mg daily, dapsone, 75 mg daily, and cyclophosphamide, 50 mg 3 times daily (Fig 1, *B*; Table I). We have been reluctant to withdraw adjunctive immunosuppressive therapy, given the severity of disease in this patient, and we recognize the potential synergy of ongoing prednisone, dapsone, and cyclophosphamide therapies with ocrelizumab.

DISCUSSION

Anti-CD20-targeted therapies cause B-cell depletion, which is postulated to reduce circulating anti-desmoglein autoantibodies (desmoglein-1 and desmoglein-3) in PV. Rituximab, a first-generation, chimeric mouse-human, anti-CD20 monoclonal antibody, is the only targeted immunotherapy approved for PV. Rituximab amplifies the rates of clinical remission and survival dramatically.[4] Unfortunately, its chimeric makeup may contribute to drug-antibody formation and allergy.[5] Ocrelizumab, a second-generation, recombinant, anti-CD20 monoclonal antibody with a humanized IgG-1 tail, binds to an overlapping but unique epitope with increased affinity. As such, ocrelizumab appears to have favorably lower immunogenicity.[6]

In this case report, the rapid and sustained response to ocrelizumab was well tolerated and demonstrates positive outcomes in the context of PV. Future research should explore the optimal dosage and comparative effectiveness with other first-line therapies. Lack of alternatives for those allergic or refractory to rituximab is challenging. Ocrelizumab offers a feasible therapeutic solution in such cases.

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Access to data and data analysis: SRC and GB had full access to all the data in the study and take responsibility for the integrity of the data.

Conflicts of interest

None disclosed.

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