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Clinical outcome and safety of rituximab therapy for pemphigoid diseases

To the Editor: The term "pemphigoid" encompasses a group of subepidermal autoimmune blistering diseases, including bullous pemphigoid (BP), mucous membrane pemphigoid, epidermolysis bullosa acquisita, and others. Fatal complications can occur from the disease or its therapy. Rituximab (RTX) has been approved by the US Food and Drug Administration for pemphigus vulgaris, but its role in pemphigoid is unclear because of the relative paucity of reported cases.

This retrospective case series included all pemphigoid patients (n = 38) at the University of Pennsylvania followed at least 1 year after RTX or until death (patient demographics can be found in Supplemental Table SI, available on Mendeley at https://doi.org/10.17632/7j5vv3rryc.1). Outcomes followed consensus definitions[1,2] (Supplemental Methods and Supplemental Table SII, available on Mendeley at https://doi.org/10.17632/7j5vv3rryc.1). The primary endpoint was complete remission (CR). Secondary endpoints were CR off therapy (CROT), corticosteroid dose, relapse, serious adverse events, and autoantibody titers.

RTX outcomes are detailed in Table I and Supplemental Table SIII (available on Mendeley at https://doi.org/10.17632/7j5vv3rryc.1). Overall, 29 of 38 pemphigoid patients (76%) achieved CR after a median of 1 RTX cycle, with a median time to CR of 14.3 months (95% confidence interval, 9.7-44.1). Considering the more rigorous endpoint of CROT, 15 of 38 patients (39%) achieved CROT after a median of 2 RTX cycles. No substantive difference in CR/CROT rates was observed among pemphigoid subtypes. CR/CROT was achieved by 53%/27% versus 52%/9% of patients who received a rheumatoid arthritis dose (n = 15) versus a lymphoma dose (n = 23) for the first RTX cycle ($P > .99/P = .19$). The median prednisone dose decreased from 20 to 3.5 mg/day ($P < .001$) in BP patients and from 20 to 4.5 mg/day ($P = .001$) in non-BP patients (Fig 1).

Longitudinal autoantibody titers were available for 13 BP patients. Median anti-BP180 titer decreased from 100.2 to 11.9 U/mL 12 months after RTX ($P < .05$), suggesting that anti-BP180 antibodies are predominantly produced by short-lived plasma cells (Supplemental Fig S1, available on Mendeley at https://doi.org/10.17632/7j5vv3rryc.1).

Seventeen of 29 patients (59%) relapsed a median of 6.2 months after achieving CR (Supplemental Fig S2, *A*, available on Mendeley at https://doi.org/10.17632/7j5vv3rryc.1). Surprisingly, BP patients exhibited a 4.8-fold hazard ratio for relapse (95% confidence interval, 1.34-17.4; $P = .007$) (Supplemental Figure S2, *B,* available on Mendeley at https://doi.org/10.17632/7j5vv3rryc.1), perhaps because minimal therapy was tapered in 67% of BP versus 17% of non-BP patients and relapses occurred in 8 of 9 pemphigoid patients (89%) who tapered doses of minimal therapy compared with 3 of 9 (33%) who maintained minimal therapy doses ($P < .05$).

Additional RTX cycles were prescribed to improve outcome or treat relapse (Supplemental Table S3 available on Mendeley at https://doi.org/10.17632/7j5vv3rryc.1). One hundred percent of patients who relapsed after achieving CR (n = 8) and 54% who received RTX to improve response (n = 13) attained CR after the second RTX cycle, indicating that outcomes are significantly different based on the indication for retreatment ($P = .02$).

Table I. Treatment parameters and outcomes

	Cycle 1 (n = 38)	Cycle 2 (n = 21)	Cycle 3 (n = 11)	Cycle 4 (n = 4)	Overall best response (n = 38)
Pemphigoid subtype					
Bullous pemphigoid	21	11	6	2	21
Mucous membrane pemphigoid	9	3	2	2	9
Other pemphigoid	8	7	3	0	8
Dose					
Lymphoma	23	16	9	4	54
Rheumatoid arthritis	15	5	2	0	22
Purpose of treatment					
Improve outcome	—	13	3	2	18
Treat relapse after achieving CR	—	8	8	2	18
Clinical outcome, n (%)					
Any remission	25 (66)	16 (76)	8 (73)	3 (75)	31 (82)
CR	20 (53)	15 (71)	8 (73)	2 (50)	29 (76)
CROT	6	11	6	1	15 (38)
CRMT	14	4	2	1	14 (37)
Partial remission	5 (13)	1 (5)	0 (0)	1 (25)	2 (5)
PROT	1	0	0	0	0 (0)
PRMT	4	1	0	1	2 (5)
Nonresponders, n (%)	13 (34)	5 (24)	3 (27)	1 (25)	7 (18)
Relapse after achieving CR, n/N (%)	14/20 (70)	10/15 (67)	5/7 (71)*	0/2 (0)	17/29 (59)
Median time to relapse after CR, mo	4.7	7.1	15.4	—	6.2
Median time from previous cycle, mo (range)	—	8.6 (5.2-54.8)	14.6 (6.5-26.5)	14.6 (6.3-17.1)	—

CR, Complete remission; *CRMT*, complete remission on minimal therapy; *CROT*, complete remission off minimal therapy; *PRMT*, partial remission on minimal therapy; *PROT*, partial remission off minimal therapy.
*One patient in CRMT was excluded because of receiving another rituximab cycle to improve outcome.

Of 7 infectious serious adverse events in 5 patients (13%), 5 occurred in patients receiving concomitant prednisone ≥7.5 mg/day and/or adjunctive immunosuppressives (Supplemental Table S4, available on Mendeley at https://doi.org/10.17632/7j5vv3rryc.1). Two deaths (primary central nervous system lymphoma, heart failure) were deemed unrelated to RTX.

Collectively, these data indicate RTX is effective in inducing CR/CROT in 76%/39% of pemphigoid patients and suggest that its primary therapeutic benefit is its steroid-sparing effect. No dose-based difference in RTX efficacy was observed. Relapse after achieving initial CR occurs in most patients (59%) but might be reduced through maintenance therapy with low-dose prednisone or dapsone. These data guide clinical expectations for the use of RTX in pemphigoid and may help to inform the design and endpoints of future prospective clinical trials.

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Conflicts of interest: Dr Payne is a co-founder and equity holder in Cabaletta Bio, Inc, focused on targeted immunotherapy of pemphigus. She is an inventor on patents licensed by Novartis and Cabaletta Bio for cellular immunotherapy of autoimmune diseases and has previously served as a consultant for Syntimmune, Inc. These organizations had no involvement in the research reported in this study. Dr Tovanabutra has no conflicts of interest to declare.

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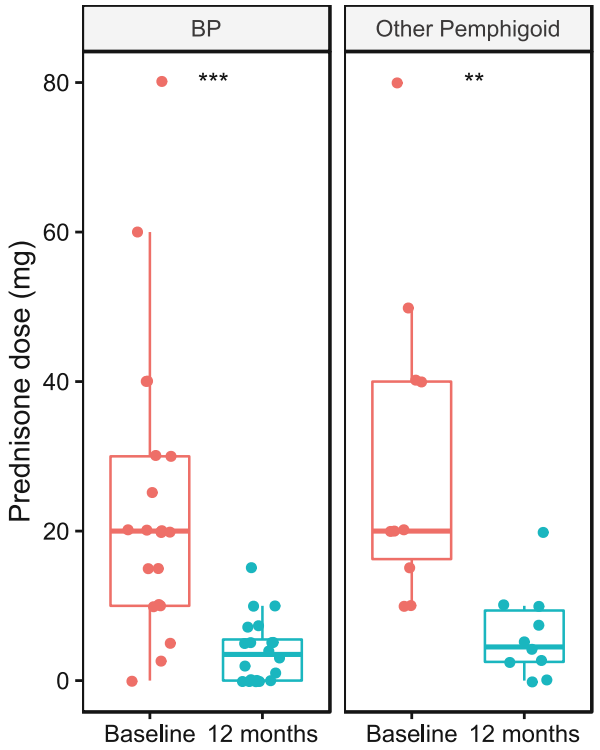

Fig 1. Rituximab is an effective steroid-sparing therapy in pemphigoid. Significant reduction in daily prednisone dose 12 months after the first cycle of rituximab in patients with bullous pemphigoid (BP) and other pemphigoid diseases. $^{*}P \leq .05$; $^{**}P \leq .01$; $^{***}P \leq .001$; ns, not significant compared with baseline values.

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Hidradenitis suppurativa encounters in a national electronic health record database notable for low dermatology utilization, infrequent biologic prescriptions, and frequent opiate prescriptions

To the Editor: Hidradenitis suppurativa (HS) is an understudied disease. Our objective was to characterize HS encounters, including providers seen, medications prescribed, and procedures performed, which to our knowledge have not previously been reported.

We performed a cross-sectional study of encounters using a random sample of the OptumInsights Electronic Health Record Database (previously Humedica[1-3]; Optum Inc, Eden Prairie, MN) from January 2007 to June 2017. Eligible encounters had an HS diagnosis code (*International Classification of Diseases* [ICD] Ninth Clinical Modification [ICD-9] 705.83, and Tenth Clinical Modification [ICD-10] L73.2) and specified a setting (eg, outpatient, inpatient) or had a prescription written. We compared nonantibiotic systemics (listed in Table I) before and after United States Food and Drug Administration approval of adalimumab and compared provider specialty and opiate prescriptions in HS vs psoriasis (defined by ICD-9 696.1, ICD-10 L40.0-40.4, L40.8, or L40.9) using χ^2 tests.

In outpatient visits without procedures, we tested whether a dermatology encounter was associated with a nonantibiotic systemic or opiate prescription using multivariable logistic regression, adjusted for age, sex, race, and region, and using generalized estimating equations to account for patients with multiple encounters. To further address potential within-patient correlations, we performed bootstrapped sensitivity analyses with 100 replications. Finally, we performed a sensitivity analysis of patients with 2 or more HS diagnoses, as the positive predictive value of a single diagnosis is 77% to 79%.[4,5]

In our data set of approximately 7.7 million patients, 22,331 encounters in 8539 patients met inclusion criteria. Patient demographics are reported in Table II. Encounter characteristics (setting, provider, medications, and procedures) are reported in Table I. In HS, 20.3% of encounters were with a dermatology provider compared with 49.0% of psoriasis encounters ($P < .001$).

The 10 most common prescriptions written were doxycycline, topical clindamycin, sulfamethoxazole-trimethoprim, hydrocodone-acetaminophen, cephalexin, oral clindamycin, oxycodone-acetaminophen, minocycline, amoxicillin-potassium clavulanate, and topical mupirocin. Use of nonantibiotic systemic medications was low (2.7%) but increased after United States Food and Drug Administration approval of adalimumab ($P = .001$). In total, 18.1% of patients received an opiate prescription during an HS encounter compared with 8.5% of psoriasis patients ($P < .001$). In outpatient visits without skin procedures, seeing a dermatology provider had an odds ratio of 0.23 (95% confidence interval, 0.17-0.31) for opiates and an odds ratio of 6.44 (95% confidence interval, 4.87-8.52) for nonantibiotic systemic medications. When we performed bootstrapped sensitivity analyses, the odds ratios were similar.