



Assessing Disease Outcome Measures in Bullous Pemphigoid on Standard-Of-Care Therapies

Emily F. Cole¹, Taryn DeGrazia¹, Yuxian Sun², Yuan Liu³ and Ron J. Feldman¹

Bullous pemphigoid (BP) is an autoimmune blistering disease resulting in pruritus and cutaneous blistering. Longitudinal studies characterizing the disease course of patients with BP on conventional therapy are lacking. We sought to characterize the changes in disease activity and pruritus of patients with BP on standard-of-care treatments. We conducted a retrospective cohort study on patients with BP on standard-of-care therapy. Generalized Estimating Equations were used to estimate the mean and standard errors for Bullous Pemphigoid Disease Activity Index (BPDAl) total activity score, BPDAl pruritus component score, and anti-BP180 autoantibody levels (BP180) over time. A total of 80 patients with BP showed consistent reductions in BPDAl total activity score and BPDAl pruritus component score, with a nadir at 4 months. BP180 decreased over time, with the largest reductions at 6 and 9 months. Median partial/complete remission was at 6.7 months, with relapses at a median time of 15.9 months. Receiving operating characteristic analysis determined an optimal BPDAl total activity score cutoff of 3.3 to discriminate partial/complete remission incidence (area under the curve = 0.895, sensitivity = 0.844, specificity = 0.78). In conclusion, in patients with BP on standard-of-care therapy, a natural course of BPDAl total activity score and BPDAl pruritus component score over time was comprehensively projected. BPDAl \leq 3.3 was associated with partial/complete remission. These results provide reference data to guide future clinical trial design for BP.

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INTRODUCTION

Bullous pemphigoid (BP) is a rare, subepidermal autoimmune blistering disease that results in debilitating symptoms, including pruritus and cutaneous blistering, with a significant impact on QOL. Standard-of-care therapies generally consist of conventional immune-suppressing medications with limited data regarding treatment course and factors influencing disease outcome over time.

The Bullous Pemphigoid Disease Area Index (BPDAl) is a clinical assessment tool that provides objective disease activity and subjective pruritus scores, has demonstrated excellent inter-rater reliability, and correlates with QOL measures specific to autoimmune blistering diseases (Murrell et al., 2012; Patsatsi et al., 2017; Wijayanti et al., 2017). Few studies have evaluated the disease course of BP using a validated clinical measure such as BPDAl, thus making optimal clinical trial designs challenging. In this study, we retrospectively characterized the disease course of patients

with BP on standard-of-care therapies evaluating BPDAl and anti-BP180 autoantibodies (BP180) to inform appropriate clinical outcomes.

RESULTS

The study population included 80 patients with BP with baseline demographic characteristics shown in Table 1. This cohort was predominantly female (57.5%) with a mean age of 73.5 ± 11.8 years. The majority of patients were white (62.5%), and clinical status was divided into those who achieved and maintained partial/complete (P/C) remission (40.0%), those who achieved P/C remission and relapsed (32.5%), and those who never achieved P/C remission (27.5%). The most common systemic therapies were prednisone (85.0%), followed by rituximab (28.8%) and mycophenolate mofetil (30.0%). On the basis of the raw data, the greatest improvement from baseline in BPDAl total activity score (TAS) occurred at month 4 with median scores from 16.8 (interquartile range [IQR] = 6.9–36.6) to 3.6 (IQR = 2.0–5.9) with a percentage reduction of 78.6%. Figure 1 was based on the estimation from the Generalized Estimating Equations (GEE) model; we observed a consistent decline in BPDAl TAS over a 12-month period. The difference between month 4 (11.7 ± 2.7) and baseline (29.1 ± 2.6) was statistically significant ($P < 0.001$). At the time of this study, there were no validated severity bands for mild to moderate BPDAl TAS; thus, to evaluate the differences in baseline severity, patients were divided into two groups by the median baseline BPDAl TAS. A similar effect was seen but to a greater degree in patients with more severe disease at baseline, with the median group mentioned earlier having an 88.1% BPDAl TAS reduction by 4 months on the basis of raw data versus 66.7% reduction in the group with scores below the median

¹Department of Dermatology, School of Medicine, Emory University, Atlanta, Georgia, USA; ²Clinical Center on TB, Beijing Chest Hospital, Capital Medical University, Beijing, China; and ³Winship Cancer Institute, Emory University, Atlanta, Georgia, USA

Correspondence: Ron J. Feldman, Department of Dermatology, School of Medicine, Emory University, 1525 Clifton Road Northeast, Atlanta, Georgia 30322, USA. E-mail: ron.j.feldman@emory.edu

Abbreviations: BP, bullous pemphigoid; BPDAl, Bullous Pemphigoid Disease Area Index; GEE, Generalized Estimating Equations; IQR, interquartile range; PCS, pruritus component score; P/C, partial/complete; TAS, total activity score

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Table 1. Demographic and Clinical Characteristics of the Study Population at Baseline

Clinical Values	All Patients (N = 80)
Age, y	73.5 ± 11.8
Sex	
Male	34 (42.5%)
Female	46 (57.5%)
Race	
White	50 (62.5%)
Black	27 (33.8%)
Asian	3 (3.7%)
Remission status	
Achieved and maintained P/C remission	32 (40.0%)
Achieved P/C remission and relapsed	26 (32.5%)
Never achieved P/C remission	22 (27.5%)
Therapies ¹	
Prednisone	68 (85.0%)
Rituximab	23 (28.8%)
Mycophenolate mofetil	24 (30.0%)
Methotrexate	9 (11.3%)
Dapsone	9 (11.3%)
Azathioprine	10 (12.5%)
Doxycycline	16 (20.0%)
IVIg	3 (3.8%)
Sulfasalazine	3 (3.8%)
Other immune modulating therapy	12 (15.0%)
BPDAI TAS	16.8 (6.9–36.6)
BPDAI PCS	20.0 (9.0–26.0)
BP180, U/ml	41.0 (0–115.0)
BP230, U/ml	0 (0–38.0)
Duration of follow-up, mo	15.05 (6.0–34.5)

Abbreviations: BPDAI, Bullous Pemphigoid Disease Area Index; PCS, pruritus component score; P/C, partial/complete; Q, quartile; TAS, total activity score.

Data are presented as mean ± SD for normally distributed variables, median (Q1, Q3) for asymmetrically distributed variables, or count (percentage) for categorical variables. BPDAI scores were calculated according to Murrell et al. (2012).

¹Sums to greater than 100% owing to patients on dual therapy.

(Figure 2). Overall, 60.6% of patients achieved a 50% reduction in BPDAI TAS, and 45.5% of patients achieved a 75% reduction by 4 months with continued improvement to month 12. No significant differences were noted between treatment modalities. BPDAI TAS was significantly higher at baseline in black patients than in white patients (25.0 [IQR = 8.0–44.3] vs. 12.9 [IQR = 5.3–24.6], *P* = 0.035) with no significant difference at month 4. The median BPDAI TAS scores at the time of relapse were 7.3 (2.3–12.0) compared with those of one visit before (median 0 [IQR = 0–2.0]). A receiver operating characteristic analysis determined an optimal BPDAI cutoff of 3.3 to discriminate P/C remission incidence (area under the curve = 0.895, sensitivity = 0.844 [95% confidence interval = 0.787–0.891], specificity = 0.780 [95% confidence interval = 0.731–0.824]).

The median BPDAI pruritus component score (PCS) at baseline was 20.0 (IQR = 9.0–26.0) with decreases from baseline until month 4 (8.0 [IQR = 0–15.0]) and subsequent stabilization until 12 months. The percentage reduction of BPDAI PCS at month 4 was 42%, with a similar trend

observed in patients above and below the median. On the basis of a GEE model (Figure 3), the estimated mean and standard error were 18.5 (1.2) at baseline and 10.3 (1.6) at month 4 (*P* < 0.001).

Overall, 40.4% of patients achieved 50% reduction in BPDAI PCS, and 21.15% of patients achieved 75% reduction by 4 months. BPDAI PCS was positively correlated with BPDAI TAS (*r* = 0.43; *P* < 0.001), with correlations significant within subgroups of patients who received prednisone (*r* = 0.43; *P* < 0.001), adjuvant therapy (*r* = 0.47; *P* < 0.001), and previous rituximab infusion (*r* = 0.46, *P* < 0.001). Pruritus was significantly higher among black patients at baseline (24.5 [IQR = 17.5–29.5] vs. 17.0 [IQR = 8.0–23.0], *P* = 0.042) and at month 4 (17.0 [IQR = 15.0–26.0] vs. 3.0 [IQR = 0–10.0], *P* = 0.010).

The median baseline BP180 in our cohort was 41.0 U/ml (IQR = 0–115.0). BP180 was found to consistently decrease from baseline, with nadirs at month 6 (21.00 [IQR = 12.0–29.0]) and month 9 (0, IQR = 0–14.0). On the basis of the GEE model, Figure 4 shows these trends in BP180 over time. BP180 significantly correlated with BPDAI TAS (*r* = 0.62; *P* < 0.001) and BPDAI PCS (*r* = 0.31; *P* < 0.001). BP180 in black patients was significantly higher than that in white patients at baseline (103.0 [IQR = 15.4–175.0] vs. 22.0 [IQR = 0–81.0], *P* = 0.039) with no difference at month 4. On the basis of the raw data, the median baseline BP230 was 0 (IQR = 0–38.), with no consistent pattern observed in changes over time, likely owing to fewer observations. Figure 5 shows the GEE model for BP230 over time; note that months 1 and 2 were binned owing to scarce data points. There were no differences in BPDAI TAS, BPDAI PCS, BP180, or BP230 by clinical status at baseline or month 4; patients who did not achieve P/C remission trended toward higher BPDAI TAS scores at month 4, although this did not reach statistical significance (Table 2).

DISCUSSION

Owing to the limited number of longitudinal studies evaluating BPDAI over time, this study sought to characterize the disease course of patients with BP on standard-of-care therapies. In this retrospective longitudinal study of 80 patients with BP, we observed consistent reductions in BPDAI TAS/PCS and BP180 over a 12-month period, with initial nadirs at 4 and 6 months, respectively. This trend was consistently observed despite the use of different systemic therapies, including rituximab. Patients with more severe baseline disease tended to have greater and more rapid reductions in BPDAI TAS, likely influenced by the use of more aggressive immunomodulatory therapies; however, the nadir at 4 months was consistently noted (Figure 2). These findings suggest that 16 weeks is an appropriate duration to detect a clinical response.

Patients with BP describe significant QOL impact from itching, and the use of itching as an outcome in BP studies is lacking (Cole et al., 2020; Sebaratnam et al., 2013). BPDAI PCS is a subjective measurement of itch using a visual analog scale and is a summary of scores over the past 24 hours, week, and month. Similar to BPDAI TAS, we found consistent reductions in BPDAI PCS by 4 months. However,

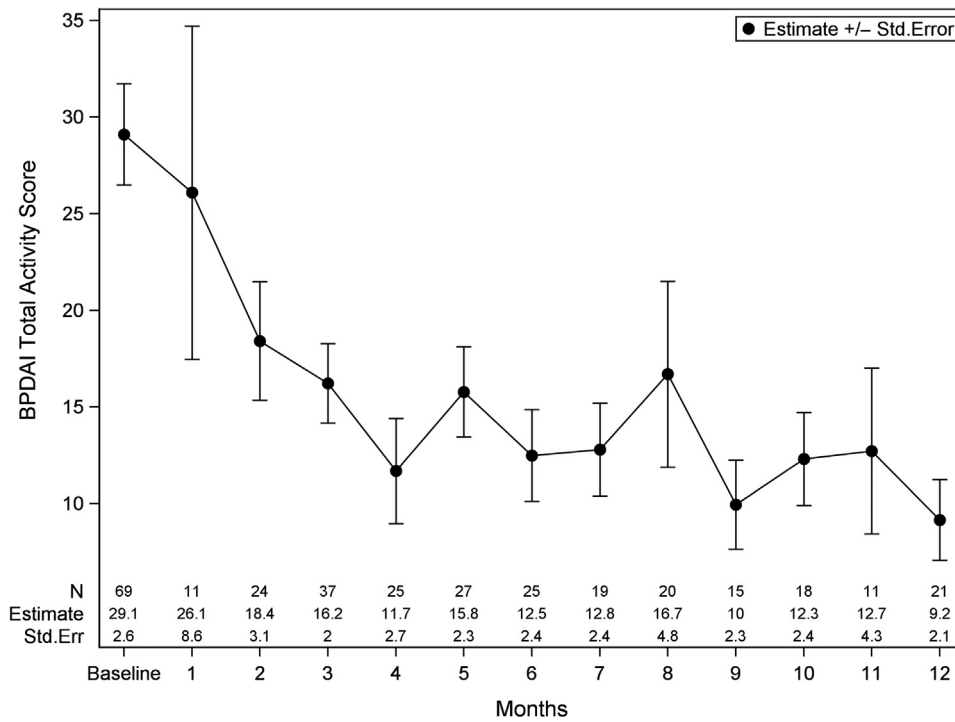


Figure 1. BPDAI TAS from baseline to 12 months. Data are presented as estimate \pm Std. Err from the GEE model, which was controlled for age, sex, and race. BPDAI, Bullous Pemphigoid Disease Area Index; GEE, Generalized Estimating Equations; Std. Err, standard error; TAS, total activity score.

over the 12-month period, patients with low BPDAI TAS surprisingly still experienced a persistent itch burden. This result suggests possible consequences of other factors in addition to disease activity, but future studies will need to clarify this discrepancy. In general, BPDAI PCS is a simple measurement tool to provide information on subjective itch burden and may be appropriate as secondary outcomes in clinical trials.

We attempted to compare the clinical factors associated with P/C remission and relapse at baseline and at the 4-month time period (Table 2). The median time to relapse was 15.9 months (IQR = 12.4–26.9), and no correlations were observed between baseline characteristics and predictive of relapse, including sex, age, BPDAI PCS, BP180, and BP230, which is in contrast to the findings of a previous study suggesting increased baseline BP180 being predictive of relapse

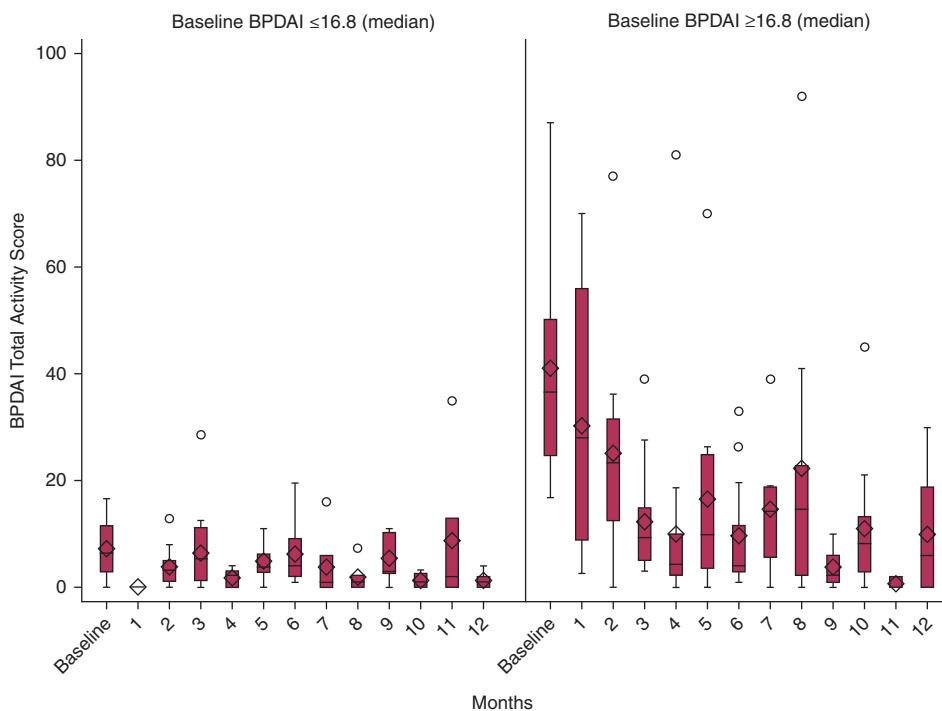
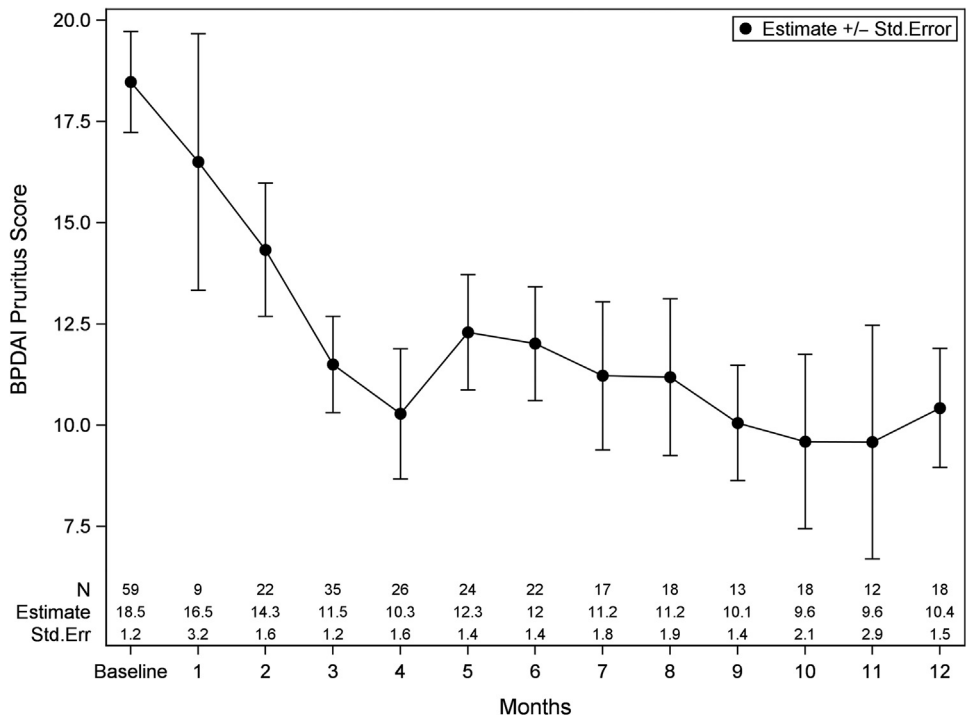


Figure 2. BPDAI TAS from baseline to 12 months by baseline BPDAI TAS. Note: groups were defined as BPDAI total activity score at baseline above and below the median (16.8, IQR = 6.9–36.6); data are presented as estimate \pm Std. Err from the raw data. BPDAI, Bullous Pemphigoid Disease Area Index; IQR, interquartile range; Std. Err, standard error; TAS, total activity score.

Figure 3. BPDAl pruritus score from baseline to 12 months. Data are presented as estimate ± Std. Err from the GEE model, which was controlled for age, sex, and race. BPDAl, Bullous Pemphigoid Disease Area Index; GEE, Generalized Estimating Equations; PCS, pruritus component score; Std. Err, standard error.

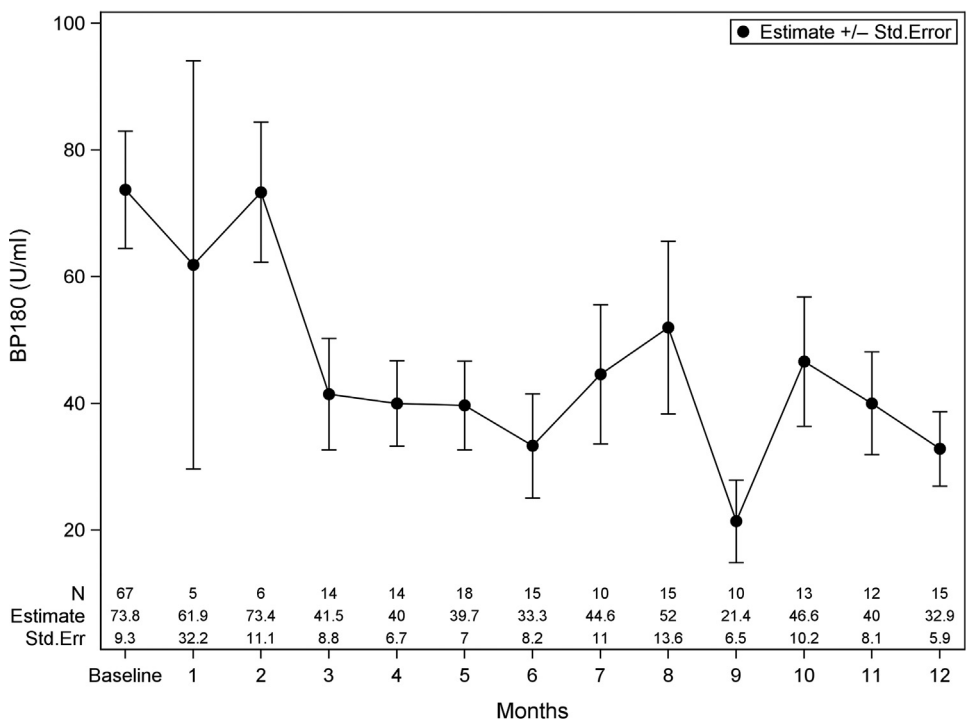


(Koga et al., 2018). The BPDAl TAS was noted to increase at the time of relapse from a median of 0 to 7.3, which is consistent with the findings of previous studies showing worsening disease associated with an increase in BPDAl TAS greater than 3 (Wijayanti et al., 2017). The median time to P/C remission was 6.7 months (IQR = 3.9–11.5), and BPDAl TAS at 4 months trended toward significance in those patients who achieved P/C remission ($P = 0.080$). Additional studies

with larger sample sizes are needed to clarify this observation (Patsatsi et al., 2017; Sebaratnam et al., 2013; Wijayanti et al., 2017). Previous studies evaluating change in BPDAl over time had defined a cut-off value for severe disease as BPDAl TAS > 56, and more recently, an international validation study refined further cutoffs for both mild (0–20) and moderate (20–56) disease, whereas banding for remission was lacking (Lévy-Sitbon et al., 2014; Masmoudi et al.,

Figure 4. Anti-BP180 IgG antibody titer from baseline to 12 months.

Note: data are presented as estimate ± Std. Err from the GEE model, which was controlled for age, sex, and race. GEE, Generalized Estimating Equations; Std. Err, standard error.



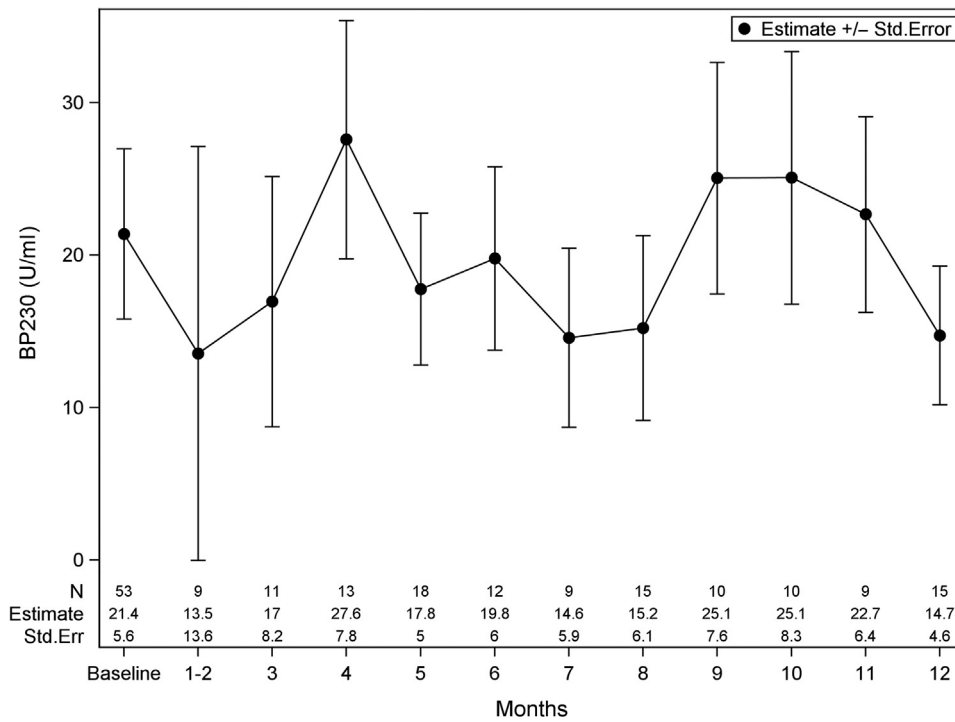


Figure 5. Anti-BP230 IgG antibody titer from baseline to 12 months.
Note: data are presented as estimate \pm Std. Err from the GEE model, which was controlled for age, sex, and race. Months 1 and 2 were binned owing to the scarce data points. GEE, Generalized Estimating Equations; Std. Err, standard error.

2021). Although our dataset did not allow for defining specific cutoffs for BPDAl severity, our data do suggest a BPDAl TAS score of 3.3 as a precise predictor of P/C remission for potential use in clinical trials.

Regarding race, BPDAl TAS and BP180 were significantly higher in black patients at baseline than in white patients, with normalization by 4 months with treatment. Interestingly, BPDAl PCS was persistently elevated in black patients compared with that in whites, independent of therapy. These findings are to our knowledge previously unreported in BP and mirror previous reports suggesting a greater burden of pruritus in non-whites, particularly in African Americans (Shaw et al., 2017). Additional studies are warranted to explore the impacts of race on clinical outcomes in BP.

Limitations of this study included a single site in a tertiary referral academic center, the retrospective nature of the study with missing data, and a relatively small number of patients with severe BP. However, the relative diversity of our patient

population was informative. In conclusion, we observed consistent reductions in BPDAl TAS/PCS and BP180 in patients treated with standard-of-care therapy, and this study provides important data to further inform the study design of much-needed future clinical trials.

MATERIALS AND METHODS

This study was approved by the Emory Institutional Review Board (#IRB00054860). After obtaining Institutional Review Board approval, a retrospective chart review was performed on 142 patients with a clinical diagnosis of BP treated at the Autoimmune Blistering Disease clinic, Emory University between June 15, 2012 (when the BPDAl was adopted) and February 1, 2019. All subjects were aged ≥ 18 years with a histopathologic and/or serologic diagnosis of BP. In addition, patients were required to have at least two visits to be included in this study. Some patients were initially seen at our institution but not at the autoimmune blistering disease specialty clinic and did not have documented BPDAl scores at baseline. Clinical records were queried for demographic information,

Table 2. Univariate Associations of Clinical Factors by Clinical Status at Baseline and Month 4

Clinical Factor	Baseline				Month 4			
	Never Achieved P/C Remission	Achieved P/C Remission and Relapsed	Achieved and Maintained P/C Remission	P-Value	Never Achieved P/C Remission	Achieved P/C Remission and Relapsed	Achieved and Maintained P/C Remission	P-Value
BPDAl TAS	21 (7–47.6)	16.1 (8–35)	16.9 (5–40)	0.816	5.9 (5–81)	3.9 (3–5)	2.9 (1–4.8)	0.080
BPDAl PCS	18 (11–26)	21 (9–28)	19 (8–24)	0.620	0 (0–30)	9.5 (6–15)	3 (0–15)	0.592
Anti-BP180 IgG (U/ml)	50 (0–88)	62 (12–147)	19 (0–107)	0.573	18.5 (10–27)	12.5 (10–15)	45 (26–54)	0.288
Anti-BP230 IgG (U/ml)	0 (0–0)	0 (0–29)	0 (0–50)	0.071	0 (0–0)	36.5 (19–54)	21 (10–40)	0.351

Abbreviations: BPDAl, Bullous Pemphigoid Disease Area Index; PCS, pruritus component score; P/C, partial/complete; Q, quartile; TAS, total activity score. At baseline: never achieved P/C remission, n = 22; achieved P/C remission and relapsed, n = 26; and achieved and maintained P/C remission, n = 32. Data are presented as median (Q1, Q3); nonparametric values calculated using the Kruskal–Wallis test.

treatments, clinical parameters (BPDAI TAS and BPDAI PCS), and anti-BP180/BP230 autoantibodies (BP180/BP230). BPDAI and clinical status (baseline, flare, or P/C remission) were scored in accordance with consensus definitions (Murrell et al., 2012). A total of 80 patients with BP on standard-of-care therapies were included in the study. Of note, 20 of these patients treated with rituximab were included in a previous publication (Polansky et al., 2019). All patients included in this study were prescribed medium-to-high potency topical corticosteroids in addition to any systemic therapies as is standard in our clinical practice.

Statistical analysis was conducted using SAS, version 9.4, and SAS macros developed by Biostatistics and Bioinformatics Shared Resource at Winship Cancer Institute (Atlanta, GA) (Liu et al., 2018). Descriptive statistics (mean, SD, median, 25th and 75th percentile (quartile 1–quartile 3), range, count, and percentage) were summarized for baseline characteristics. Univariate analysis comparing clinical factors by clinical status at baseline and month 4 was performed using Kruskal–Wallis test. Because clinical parameters were measured longitudinally over multiple clinical visits, GEE (Hardin, 2003), a marginal model with a robust sandwich variance estimator, was used to estimate the population-averaged means and standard errors at each time, controlling for baseline race, sex, and age. The correlation structure among the repeated visits for the same patients was determined that minimized the Akaike's information criterion. A receiver operating characteristic analysis (Fawcett, 2006) was calculated to determine an optimum cutoff (Youden's index) for BPDAI TAS using P/C remission status as the outcome. Pearson's correlation coefficient was used to describe the association between two continuous measurements, for example, BPDAI TAS and BP180. $P \leq 0.05$ was considered statistically significant.

Data availability statement

No large datasets were generated or analyzed during this study. Limited datasets necessary to interpret and/or replicate data in this paper are available on request to the corresponding author.

ORCIDiDs

Emily F. Cole: <http://orcid.org/0000-0002-3043-3152>

Taryn DeGrazia: <http://orcid.org/0000-0002-1537-3374>

Yuxian Sun: <http://orcid.org/0000-0002-6061-8457>

Yuan Liu: <http://orcid.org/0000-0001-8926-3058>

Ron Feldman: <http://orcid.org/0000-0001-5766-5132>

AUTHOR CONTRIBUTIONS

Conceptualization: RJF, EFC, TD; Data Curation: TD, EFC, YL; Formal Analysis: YL, YS; Investigation: TD, EFC; Methodology: RJF, EFC; Project Administration: RJF, EFC; Resources: RJF, YL; Software: YL; Supervision: RJF; Validation: YL, YS; Visualization: YL, YS; Writing - Original Draft Preparation: EFC, RJF; Writing - Review and Editing: EFC, RJF, YL

CONFLICT OF INTEREST

The authors state no conflict of interest.

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