Original Article

The Role of Anti-BP180 Antibody Monitoring in Bullous Pemphigoid: An Italian Single-Center Experience

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Abstract

Introduction: Bullous pemphigoid (BP) is the most common autoimmune blistering disorder, with anti-BP180 antibodies playing a key role in its pathogenesis and diagnosis. However, their utility in disease monitoring remains debated.

Objectives: This study evaluate the role of anti-BP180 antibody monitoring in BP management through a single-center retrospective analysis and literature review.

Methods: We analyzed 149 BP patients diagnosed between 2014 and 2024 at the Dermatology Unit, IRCCS Azienda Ospedaliero-Universitaria di Bologna. Anti-BP180 titers were measured at baseline, six months, and remission. Therapeutic responses and antibody dynamics were assessed and compared with the literature.

Results: Higher baseline anti-BP180 levels correlated with severe disease and prolonged remission times. A ≥60% reduction in titers was associated with successful therapeutic tapering and lower relapse rates. Patients with secondary BP forms exhibited lower baseline titers and faster remission.

Conclusions: Anti-BP180 monitoring serves as a valuable adjunct to clinical assessment, aiding therapeutic decisions, particularly in determining tapering timelines. Nonetheless, integrated approaches combining serological and clinical evaluations remain essential.

Introduction

Bullous pemphigoid (BP) is the most common autoimmune subepidermal blistering disorder, primarily affecting older individuals, with an increasing incidence due to improved diagnostics and aging populations [1,2]. It is characterized by tense blisters, pruritus, and erythematous plaques, with IgG autoantibodies primarily targeting BP180 (collagen XVII), a transmembrane protein crucial to dermoepidermal adhesion [3,4]. BP230, another hemidesmosomal protein, is also a target but less frequently associated with disease activity [5,6]. The detection of anti-BP180 antibodies using ELISA has become standard for diagnosis due to its high sensitivity and specificity [5,8]. However, its role in disease monitoring remains debated [9]. High anti-BP180 levels correlate with disease activity, severity, and potential relapses, suggesting that periodic monitoring could guide treatment adjustments [10-12]. Nevertheless, some studies argue that clinical evaluation remains superior for therapeutic decisions due to variability in antibody levels and a lack of consistent correlation with disease progression [9].

Objectives

This study aimed to critically assess the role of anti-BP180 antibody monitoring in BP management through a comprehensive review of the existing literature and the data from the Dermatology Clinic of the IRCCS Azienda Ospedaliero-Universitaria of Bologna. It sought to determine whether antibody level monitoring can enhance therapeutic strategies or if it poses an unnecessary burden without substantial clinical benefit.

Methods

This study was designed as a single-center retrospective observational study of patients evaluated at the Dermatology Unit, Sant'Orsola Policlinic in Bologna, attending the blistering diseases clinic for a new diagnosis of BP. Diagnosis was confirmed through clinical evaluation, histological examination, and direct immunofluorescence. Patient selection was based on the following inclusion criteria:

- New-onset BP
- Positivity for anti-BP180 and BP230 antibodies
- Dermatological evaluation between August 2014 and August 2024.

The exclusion criteria were:

- Absence of detectable anti-BP180 antibodies at t0
- Missing anti-BP180 titer measurements at t6 and at clinical remission
- Previously diagnosed BP (relapse cases).

Collected data included age, sex, anti-BP180 and BP230 antibody titers at t0 (baseline), t6 (six months), and at remission (defined as no clinical manifestation for at least six months since the withdrawal of treatment), time to remission (in months), first-line treatments (mild forms: topical/systemic steroids or tetracycline; moderate-severe forms: topical/systemic steroids plus immunosuppressants), and drug-induced, pregnancy-associated, and paraneoplastic forms. According to literature data, mild BP disease was defined as a score of 19 or less on the Bullous Pemphigoid Disease Area Index (BPDAI), moderate disease as a score of 20–56 points, and severe disease as a score of 57 or more points [13]. Antibody levels were measured using ELISA kits (U/mL), with a positivity cutoff of ≥20.

Descriptive statistics were used, with quantitative variables reported as means and standard deviations, and qualitative variables as numbers and percentages. Finally, results were compared to the existing literature on the prognostic value of anti-BP180 monitoring in BP, with a literature

review conducted via PubMed, SCOPUS, and Medline using keywords such as “anti-BP180 and bullous pemphigoid”, “diagnostic and prognostic factors in bullous pemphigoid”, “biomarkers in monitoring bullous pemphigoid,” and “anti-BP180 and bullous pemphigoid therapy response.”

Results

A total of 149 patients with a new diagnosis of BP and positivity for anti-BP180 autoantibodies were included between 01 August 2014, and 01 August 2024, comprising 82 females and 67 males. Age distribution was similar between sexes, with over 60% of patients aged >75 years (62.2% female patients and 67.2% male patients). Secondary forms of BP (drug-induced, paraneoplastic, or pregnancy-associated) represented 20.8% of the sample, with DPP-4 inhibitors (gliptins) being the most common triggering drugs (6.7%). Secondary forms were more prevalent in individuals aged >75 years (24%) and in females (61.3%).

Seventy-seven percent of patients (114/149) achieved remission within six months, while 97% achieved remission by 12 months. The mean time to remission was 7.5 months. Patients with secondary forms exhibited a shorter mean time to remission of 5 months.

The mean anti-BP180 antibody titer at t0 was 111 U/mL. Mean titers were 47 U/mL at t6 and 39 U/mL at clinical remission. Patients achieving remission within six months had a lower mean baseline titer (104 U/mL) compared to those with delayed remission (>6 months; 131 U/mL). At t6, patients in remission had a mean titer of 37 U/mL (60% reduction), while those not in remission had a mean titer of 79 U/mL (40% reduction). Finally, approximately half of the patients (52%) had negative anti-BP180 antibodies at remission, while the remaining had titers >20 U/mL.

The mean anti-BP230 antibody titer was 39 U/mL at t0, 17 U/mL at t6 and 15 U/mL at remission, with no significant baseline difference between early and late responders (39 U/mL early vs 38 U/mL, respectively).

Patients with secondary forms had lower baseline anti-BP180 titers (mean value=105 U/mL) and shorter remission times (five months) but showed no significant difference in titers at t6 or at remission compared to primary forms. Basic treatment with topical/systemic steroids or tetracycline (95/149 patients) resulted in 85% remission at t6 and was associated with lower baseline disease burden. These patients had a mean baseline titer of 102 U/mL and a remission titer of 35 U/mL. Intensive treatment (steroids associated with immunosuppressants) was administered to 54/149 patients, who had higher mean baseline titers (125 U/mL) and a lower reduction over time (mean titer of 47 U/mL at remission), with only 61% in remission at t6.

Discussion

Traditionally, the therapeutic management of BP is guided by the clinical assessment of disease severity [13]. This can be objectified through validated scoring systems used in clinical trials such as the BPDAI and the Autoimmune Bullous Skin Disorder Intensity Score (ABSIS), or more simply, by counting the number of new blisters formed per day, the presence of pruritus, and mucosal lesions [13-15]. Over the years, with the widespread use of ELISA kits to measure anti-BP180 antibodies for diagnostic purposes, interest has also grown in periodically monitoring antibody titers to determine whether they correlate with disease progression [9-12].

Numerous published studies have highlighted a correlation between anti-BP180 antibody titers and disease activity, both at onset and during the first year after diagnosis. Several research groups have suggested monitoring anti-BP180 levels to guide therapeutic decisions and to determine the

appropriate timing for tapering medications. Literature findings indicate that patients with higher anti-BP180 titers exhibit greater disease burden and require more intensive and prolonged treatments, thereby reducing their risk of severe complications, including mortality. In recent years, periodic monitoring of anti-BP180 antibodies has become established as a therapeutic guide with prognostic value [9-12].

Meta-analyses and reviews in the literature reveal that anti-BP180 antibodies significantly correlate with disease severity scores such as BPDAI and ABSIS. In particular, the meta-analysis by Chou et al. observed a moderate correlation ($r=0.56$) at the start of treatment, which became strong ($r=0.63$) after three months and remained moderate ($r=0.53$) at six months. This progression suggests that anti-BP180 levels can reflect disease evolution and serve as an auxiliary tool for guiding therapeutic decisions. Conversely, anti-BP230 antibody levels do not appear to correlate with disease activity. High anti-BP180 IgG levels at remission seem to indicate an increased risk of relapse within one year of treatment discontinuation. Furthermore, elevated anti-BP180 levels are associated with higher steroid doses, longer time to achieve clinical remission, and increased mortality rates [16].

Our clinical study also demonstrated that disease activity is accurately reflected by anti-BP180 antibody titers, with lower titers both at baseline (t0) and at remission in patients who achieved faster healing. Antibody titers at diagnosis guided therapeutic choices, allowing for less intensive treatment in patients with better clinical outcomes.

The literature also indicates that BP secondary to drugs, pregnancy, or malignancies is associated with faster healing once the triggering cause is removed, and these cases are often observed in younger patients [17-20]. The shorter remission time in secondary BP forms is likely related to the removal or resolution of the triggering factor (e.g., pregnancy resolution in pemphigoid

gestationis). In our cohort, however, the majority of secondary cases were drug-induced BP, while only one patient had pemphigoid gestationis.

We observed a shorter average healing time in induced cases (five months compared to 7.5 months for the total sample), along with lower mean serum anti-BP180 IgG levels. However, in our cohort, the average age of secondary cases was higher than that of the rest of the sample, likely due to the higher prevalence of drug-induced cases, as older patients tend to take more medications, increasing the likelihood of drug-induced BP.

Izumi et al. suggested monitoring anti-BP180 antibodies to determine when to start tapering steroids and immunosuppressants. Specifically, their group proposed initiating dose reduction after a 40% decrease in anti-BP180 titers from baseline. In our cohort, tapering began after an average 60% decrease in anti-BP180 titers from baseline, with positive therapeutic outcomes (97% remission at 12 months without relapses) [21].

Monitoring anti-BP180 antibodies in BP thus appears to be a valuable tool for managing the disease. However, this approach presents both advantages and disadvantages, which we analyze based on the existing literature and on our center's clinical experience (Table 1). The accuracy of serological monitoring could be improved by longitudinally assessing not only anti-BP180 IgG titers but also anti-BP180 IgE and other inflammatory biomarkers (IL-17 and IL-23) that reflect disease activity and severity, as suggested by recent studies [22-25].

This study presents certain limitations that should be acknowledged. First, its single-center retrospective design may limit the generalizability of the findings to other populations and clinical settings. The study was conducted at a tertiary referral center, which could introduce selection bias, as patients with more severe or atypical presentations might be overrepresented. Second, while anti-BP180 antibody levels were measured at defined time points (baseline, six months, and

remission), more frequent measurements could have provided a more granular view of antibody dynamics and their correlation with disease activity. The absence of longitudinal data on other potential biomarkers, such as anti-BP180 IgE or inflammatory cytokines (e.g. IL-17 and IL-23), further limits the comprehensiveness of our findings. Moreover, we did not collect the BPDAI score for the less recent patients, undermining the possibility of correlating anti-BP180 antibody titers and BPDAI. Finally, variability in ELISA test results, influenced by assay conditions and inter-laboratory differences, may also affect the reproducibility of our findings. Prospective multicenter studies with standardized protocols are necessary to validate our observations and enhance the clinical utility of anti-BP180 monitoring in BP management.

Conclusions

In conclusion, serological monitoring of BP180 antibodies appears to be a valuable complementary tool to clinical assessment in the management of patients with BP. Specifically, in real-life practice, it proves useful in determining when to initiate therapeutic tapering. However, it is essential to adopt an integrated approach that takes into account both antibody titers and other clinical indicators, such as the number of new blisters per day, their size, duration, and response to topical therapy, to optimize patient care in this complex disease. Further research is needed to confirm these findings and establish standardized protocols for the clinical use of anti-BP180 antibodies. Future prospective studies measuring anti-BP180 antibody titers in parallel with disease severity scores (BPDAI and ABSIS) will be necessary to define the percentage reduction in anti-BP180 antibody titers beyond which therapy can be discontinued with minimal risk of relapse.

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Table 1. Advantages and disadvantages of Anti-BP180 monitoring in bullous pemphigoid patients.

Advantages	**Disadvantages**
Disease Monitoring: Anti-BP180 antibodies are considered biomarkers of bullous pemphigoid activity. Their presence correlates with disease pathogenesis, inflammation levels, and the development of new blisters.	Variability of Results: Anti-BP180 antibody levels can vary significantly among patients and over time, making it difficult to establish a universal threshold for disease monitoring. This variability complicates results interpretation and clinical management.
Assessment of Therapeutic Response: Monitoring anti-BP180 antibody levels provides useful information on treatment response. A decrease in antibody levels often	Seronegative Patients and Outliers: A significant percentage of bullous pemphigoid patients (25% in our clinical study) have undetectable anti-BP180 antibodies, making

corresponds to reduced disease severity, enabling clinicians to adjust therapies more effectively.	serological monitoring impossible in these cases. Additionally, a minority of patients maintain positive anti-BP180 titers even during complete clinical remission, reducing the utility of serological monitoring compared to clinical assessment in guiding therapy.
Prediction of Relapses: Continuous antibody surveillance helps identify patients at risk of relapse, allowing for preventive interventions. This is particularly relevant in patients with a history of frequent relapses.	Costs and Accessibility: Regular antibody monitoring requires resources and facilities that may not be available in all healthcare settings. The associated costs can be a significant burden for patients and healthcare systems, especially in resource-limited settings.
	False Negatives and Positives: Anti-BP180 antibody tests can yield false negative or positive results, affecting therapeutic decisions. This risk underscores the need for integrated clinical evaluation to avoid management errors.