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Effectiveness of Dupilumab and Omalizumab in Bullous Pemphigoid: A Nationwide Retrospective Cohort Study

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ABSTRACT

Bullous pemphigoid (BP) is the most common autoimmune blistering skin disease worldwide. In the difficult-to-treat BP or if standard therapies are contraindicated, the use of biologics may be also considered although there is no strong evidence supporting their use. This study aimed to investigate clinical and diagnostic findings as well as treatment outcomes among patients diagnosed with BP and undergoing omalizumab or dupilumab in a real-world setting. A multicenter retrospective cohort study was performed across 15 Italian tertiary referral hospital. Medical records of 2435 BP patients were screened, identifying 58 (2.3%) Caucasian patients who

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met the inclusion criteria. Within this study population, 39 (67.2%) were treated with dupilumab and 19 (32.8%) received omalizumab. Disease control was achieved in 90.6% of dupilumab-treated patients and complete remission on minimal therapy was observed in 71.0%. Omalizumab-treated patients achieved disease control in 77.8% of cases and 64.7% obtained complete remission on minimal therapy. Log-rank test comparing relapse rate between treatment groups was not significant ($p = 0.58$). Finally, parameter estimates associated with the fixed effect of time were consistently negative, indicating a generally significant ($p = < 0.05$) decrease in scores over time for patients treated with both biologics. This cohort of patients undergoing dupilumab or omalizumab adds to the existing evidence concerning the effectiveness of biologic agents in BP. Both biologics seem to be promising treatment adjuvants in the management of BP, with dupilumab showing a descriptive trend toward better outcomes.

1 | Introduction

Bullous pemphigoid (BP) is the most common autoimmune blistering skin disease worldwide [1]. Conventional therapies are mostly based on high-potency topical corticosteroids, oral prednisone or immunosuppressive drugs such as methotrexate, azathioprine, or mycophenolates [2]. In the difficult-to-treat BP, or if standard therapies are contraindicated, the use of biologics may be also considered, although there is no strong evidence supporting their use [3]. Omalizumab, a recombinant humanized monoclonal anti-Immunoglobulin (Ig) E antibody approved in asthma and chronic spontaneous urticaria (CSU), has been used as treatment of BP in previous observations [4–11]. Similarly dupilumab, a fully human IgG4 monoclonal antibody directed against the IL-4 receptor alpha (IL-4Rα), is a biologic agent that has been used to treat BP in recent years [11–21]. However, their potential role in the management of BP still remains poorly clarified. This study sought to address this knowledge gap by investigating clinical and diagnostic findings, as well as treatment outcomes, among patients diagnosed with BP and undergoing omalizumab or dupilumab in a real-world setting.

2 | Methods

2.1 | Study Design and Population

We performed a multicenter, retrospective cohort study across 15 Italian tertiary referral hospitals. Patients were eligible if aged ≥ 18 years, were diagnosed with BP according to the European Academy of Dermatology and Venereology guidelines [2] and had received omalizumab or dupilumab between January 2017 and March 2023. Patients with a follow-up period shorter than 8 weeks were excluded. Identification of eligible cases was achieved through the retrospective review of both electronic health records and specific datasets from the participating sites. The Strengthening the Reporting of Observational studies in Epidemiology (STROBE) reporting guidelines for cohort studies were followed [22].

2.2 | Data Collection

Data including demographics, medical history, disease severity, concomitant therapy with dupilumab or omalizumab, treatment outcomes and adverse events (AEs) were collected. To identify anti-BP180 and anti-BP230 IgG autoantibodies in the serum of each patient, commercial enzyme-linked immunosorbent assay (ELISA) kits (Euroimmun, Lübeck, Germany) were used, in accordance with the manufacturer instructions. A cutoff value of > 20 U/mL was used for both type of tests. Lesional skin biopsies were evaluated by hematoxylin–eosin staining. Regarding direct immunofluorescence microscopy (DIF), perilesional sections stained with fluorescein isothiocyanate-conjugated goat anti-human Ig and C3 (Kallestad Diagnostic, Chaska, MN, USA) were analyzed under a fluorescence microscope. DIF results were recorded by taking into consideration the nature of the immune deposits (IgG, IgA, IgM, and C3), the location of the immune deposits and the extent and the pattern of immune complex deposits (granular or linear). Indirect immunofluorescence (IIF) was performed on slides containing human epithelial substrate and human salt-split skin as described [23]. ELISA was also performed for each case. Disease severity was assessed by means of BP Disease Area Index (BPDAI) obtained directly from the medical records or calculated retrospectively with archival photos taken when treatment was initiated. Cutoff values of BPDAI to differentiate between mild (≤ 19), moderate (≥ 20 and ≤ 56), and severe (≥ 57) BP were applied [24]. The peak pruritus numeric rating scale (PP-NRS), ranging from 0 (no itch) to 10 points ("worst itch imaginable"), was used to evaluate itch intensity during the previous 24 h before the visit. PP-NRS has been validated in other cutaneous inflammatory diseases, such as prurigo nodularis [25] and atopic dermatitis (AD) [26]. It has been used to assess itch intensity in clinical trials [27], including the ongoing phase 2/3 randomized controlled trial LIBERTY-BP ADEPT designed to assess the efficacy and safety of dupilumab in patients with moderate-to-severe BP [28]. The impact on quality of life was assessed through the Dermatology Life Quality Index (DLQI).

2.3 | Outcomes

The primary outcome measured was the proportion of patients who achieved disease control within 8 weeks and at the end of follow-up, defined as the point in which new lesions or pruritic symptoms cease to form and existing lesions start to heal. Secondary outcomes included: (i) the rate of patients who reached complete or partial remission of disease activity on minimal or off therapy, (ii) the proportion of patients who experienced a relapse defined as the appearance of at least three new lesions (blisters, eczematous lesions, or urticarial plaques) within 1 month, more than one eczematous lesion with a diameter of more than 10 cm, urticarial plaque that did not heal within 1 week, extension of established lesions, or daily pruritus in patients who had achieved disease control, (iii) percent changes in BPDAI, PP-NRS, and DLQI, and (iv) incidence of treatment-related AEs. All the BP treatment outcomes have been defined according to the International Pemphigoid Committee recommendations [29].

2.4 | Statistical Analysis

Categorical variables were summarized using frequencies and percentages, while quantitative variables using mean, median, standard deviation, and interquartile range (IQR). Exploratory analyses were conducted to assess the following outcomes: disease control rate (DCR), treatment response, disease relapse, and patient-reported outcomes. All eligible patients were included in descriptive analysis, while inferential ones were performed on classical BP and non-bullous pemphigoid only. Group differences were evaluated using the chi-squared and Kruskal–Wallis tests for categorical and continuous numeric variables, respectively. DCR at 8 weeks and at the end of the study period, along with each level of treatment response, was evaluated in terms of frequencies and percentages of patients; a chi-squared test was applied to assess potential differences between treatment groups. Patients were censored on March 31, 2023, and discontinuation due to AEs or lack of effectiveness was considered a concurrent event. Kaplan–Meier curves, event rate and survival median were estimated for each treatment, while log-rank test and hazard ratio were calculated to estimate potential differences among groups. A mixed-effects model for repeated measures was applied to verify the effect of time (independent variable) on the scores (dependent variables), using PROC MIXED with an unstructured covariance matrix. All tests were two-sided, and $p < 0.05$ was considered statistically significant. All analyses were performed with SAS, version 9.4 (SAS Institute Inc., Cary, North Carolina, USA). Data analysis was conducted from November 15, 2023 to March 1, 2024.

3 | Results

3.1 | Study Population

At the cutoff date for this analysis, we retrospectively screened records of 2435 patients diagnosed with BP, regardless of age and gender, identifying 58 (2.3%) Caucasian patients who met the inclusion criteria. Detailed demographics, clinical presentations at diagnosis, and previous treatments are described in Tables 1 and 2. In our cohort, a greater number of subjects were treated with dupilumab ($n = 39/58$; 67.2%), with the most frequent subtype being classic BP ($n = 28/39$; 71.8%). Other subtypes were gliptin-associated BP ($n = 4/39$; 10.3%), immunotherapy-associated BP ($n = 3/39$; 7.7%), prurigo-like BP ($n = 3/39$; 7.7%), and eczematous BP ($n = 1/39$; 2.6%). Nineteen individuals ($n = 19/58$; 32.8%) received omalizumab, with the majority diagnosed with classic BP ($n = 16/19$; 84.2%). The other subtypes were prurigo-like BP ($n = 1/19$; 5.3%), urticarial BP ($n = 1/19$; 5.3%), and gliptin-associated BP ($n = 1/19$; 5.3%). The clinical reasons for selecting either biologic agent are detailed in Table S1. As for the treatment regimen, 57 (98.3%) patients underwent a standardized dosage protocol approved for AD or CSU. Specifically, this involved an initial loading dose of 600 mg, succeeded by a maintenance dose of 300 mg, administered biweekly via subcutaneous injection for those on dupilumab, and 300 mg administered every 4 weeks for patients undergoing omalizumab. In contrast, one patient under omalizumab treatment received a tailored therapeutic regimen (three administrations of 300 mg each, every 3 weeks and after 9 months, three administrations of 300 mg each, every 4 weeks), a decision that was guided by the physician's clinical judgment [8]. Throughout the study period, no patients in the cohort experienced any modifications to their medication dosage of either dupilumab or omalizumab. The effects of introducing dupilumab or omalizumab on changes in BPDAI, PP-NRS, and DLQI are summarized in Table S2.

3.2 | Classic BP and Non-Bullous Pemphigoid

3.2.1 | Dupilumab Group

Patients were predominantly female ($n = 19/32$; 59.4%), with a mean (±SD) age of 76.0 ± 14.3 years. Prior to the administration of dupilumab, patients had undergone a mean of 2.7 ± 1.2 different treatments, with a mean disease duration of 21.0 ± 21.7 months. Dupilumab was started in combination with at least one systemic therapy, with or without topical steroids, in most patients ($n = 23/32$; 71.9%). It was used as a monotherapy in eight patients (25%) and combined with only topical steroids in two patients (6.3%). Throughout the mean follow-up period of 9.7 ± 6.4 months, patients underwent a mean number of 1.2 ± 0.8 treatments specifically targeting BP, with a cumulative dose of prednisone of 1041.0 ± 1816.98 mg (Table 3). Overall, disease control was achieved in the majority of cases ($n = 29/32$; 90.6%), of which 4/32 patients (12.5%) within 4 weeks and 18/32 patients (56.2%) within 8 weeks (Figure 1a,b). One patient died due to sepsis after achieving disease control; this event was not considered related to the medication. A total of 27/31 (87.1%) patients reached complete remission, with 22/31 (71.0%) on minimal therapy and 5/31 (16.1%) off therapy. When available ($n = 25/27$; 92.5%), the mean time to complete remission was 4.9 ± 5.77 months. Partial remission on minimal therapy was achieved in 1/31 (3.2%) patients, partial remission off therapy in 1/31 (3.2%), stable disease was observed in 1/31 (3.2%), and progressive disease in 1/31 (3.2%) (Figure 2). Relapse was experienced in 3/29 (10.3%) subjects, after a mean time of 5.3 ± 4.03 months. Overall, 5/32 patients (15.6%) discontinued dupilumab: One due to BP clinical remission (3.1%), three due to treatment ineffectiveness (9.4%), and one due to an AE (3.1%).

3.2.2 | Omalizumab Group

In the omalizumab cohort, patients had a mean age of 74.8 ± 10.1 years and 9/18 (50%) were males. Prior to the administration of drug, the mean disease duration was 29.3 ± 32 months and patients had received a mean of 3.3 ± 1.8 different treatments. Omalizumab was started in combination with at least one systemic therapy, with or without topical steroids, in all the patients. During the mean follow-up of 19.8 ± 10.7 months, patients received a mean of 2.1 ± 0.87 treatments specifically targeting BP, with a cumulative prednisone dose of 3672.6 ± 3710.10 mg (Table 3). A consistent sample of patients achieved disease control ($n = 14/18$; 77.8%), of which 1/18 (5.5%) within 4 weeks and 5/18 (27.7%) within 8 weeks (Figure 1a,b). One patient was lost to follow-up after disease control. Overall, 11/17 (64.7%) patients reached complete remission on minimal therapy, while partial remission on minimal therapy was observed in 3/17 (17.6%) and stable disease in 3/17 (17.6%) patients (Figure 2). When available ($n = 7/11$; 63.4%), the mean time to complete remission was 9.6 ± 7.9 months. Relapse was observed in less than

TABLE 1 | Demographics and clinical characteristics.

	Omalizumab		Dupilumab			
	Classical BP and non bullous pemphigoid (*N* = 18)	**Gliptin-associated BP (*N* = 1)**	**Classical BP and non-bullous pemphigoid (*N* = 32)**	**Immunotherapy-associated BP (*N* = 3)**	**Gliptin-associated BP (*N* = 4)**	**Total (*N* = 58)**
Subtype, *n* (%)						
Classic bullous pemphigoid	16 (88.8%)	1 (100%)	28 (87.5%)	3 (100%)	3 (75.0%)	51 (87.9%)
Non-bullous						
Non-bullous pemphigoid (eczematous type)	0 (0.0%)	0 (0.0%)	1 (3.1%)	0 (0.0%)	1 (25.0%)	2 (3.5%)
Non-bullous pemphigoid (prurigo-like type)	1 (5.6%)	0 (0.0%)	3 (9.4%)	0 (0.0%)	0 (0.0%)	4 (6.8%)
Non-bullous pemphigoid (urticarial type)[a]	1 (5.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.7%)
Age (years)						
N	18	1	32	3	4	58
Mean (SD)	74.8 (10.1)	91.0 (.)	76.0 (14.3)	67.0 (5.00)	71.5 (5.9)	75.14 (12.4)
Median (IQR)	77.0 (70.0, 83.0)	91.0 (91.0, 91.0)	80.0 (70.0, 86.0)	67.0 (62.0, 72.0)	73.5 (67.5, 75.5)	76.0 (70.0, 83.0)
Gender, *n* (%)						
F	9 (50.0%)	1 (100.0%)	19 (59.4%)	1 (33.3%)	1 (25.0%)	31 (53.5%)
M	9 (50.0%)	0 (0.0%)	13 (40.6%)	2 (66.7%)	3 (75.0%)	27 (46.5%)
BMI						
N	7	0	20	2	4	33
Mean (SD)	24.3 (2.1)	—	24.4 (3.2)	29.7 (0.4)	26.1 (4.20)	24.9 (3.25)
Median (IQR)	24.9 (22.0, 26.2)	—	23.7 (23.0, 26.6)	29.7 (29.3, 30.0)	26.3 (22.8, 29.4)	24.7 (23.0, 27.3)
Skin biopsy consistent with BP, *n* (%)						
Yes	18 (100.0%)	1 (100.0%)	32 (100.0%)	3 (100.0%)	4 (100.0%)	58 (100.0%)

(Continues)

TABLE 1 | (Continued)

	Omalizumab		Dupilumab			
	Classical BP and non bullous pemphigoid (*N* = 18)	**Gliptin-associated BP (*N* = 1)**	**Classical BP and non-bullous pemphigoid (*N* = 32)**	**Immunotherapy-associated BP (*N* = 3)**	**Gliptin-associated BP (*N* = 4)**	**Total (*N* = 58)**
DIF positive, *n* (%)						
Yes	15 (93.8%)	0 (0.0%)	28 (96.6%)	3 (100.0%)	3 (100.0%)	49 (94.2%)
IIF positive, *n* (%)						
Yes	9 (81.8%)	1 (100.0%)	3 (60.0%)	0 (0.0%)	1 (100.0%)	14 (77.8%)
Serum anti-BP180 IgG at diagnosis, *n* (%)						
Yes	14 (82.4%)	0 (0.0%)	26 (83.9%)	3 (100.0%)	4 (100.0%)	47 (83.9%)
Serum anti-BP230 IgG at diagnosis, *n* (%)						
Yes	10 (62.5%)	0 (0.0%)	10 (33.3%)	0 (0.0%)	0 (0.0%)	20 (34.5%)
Serum IgE levels at diagnosis[b]						
N	14	1	18	1	2	36
Mean (SD)	2164.7 (3168.4)	638.1 (.)	853.5 (1199.2)	1550.0 (.)	155.0 (42.4)	1338.0 (2217.3)
Median (IQR)	786.5 (210.0, 2449.0)	638.1 (638.1, 638.1)	393.0 (180.0, 1175.0)	1550.0 (1550.0, 1550.0)	155.0 (125.0, 185.0)	485.5 (181.3, 1616.0)
Urticarial lesions at diagnosis, *n* (%)						
Yes	7 (53.8%)	0 (0.0%)	13 (46.4%)	2 (66.7%)	1 (25.0%)	23 (47.9%)
Association with immunotherapy, *n* (%)						
Nivolumab	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (33.3%)	0 (%)	1 (33.3%)
Pembrolizumab	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (66.7%)	0 (%)	1 (66.7%)
Association with gliptin, *n* (%)						
Sitagliptin	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (100.0%)	1 (25.0%)	1 (20.0%)
Linagliptin	0 (0.0%)	1 (100.0%)	0 (0.0%)	0 (0%)	2 (50.0%)	3 (60.0%)
Alogliptin	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0%)	1 (25.0%)	1 (20.0%)
Hospitalization due to BP,[c] *n* (%)						
Yes	7 (38.9%)	0 (0.0%)	4 (12.5%)	1 (33.3%)	2 (50.0%)	14 (24.1%)

(Continues)

TABLE 1 | (Continued)

	Omalizumab		Dupilumab			
	Classical BP and non bullous pemphigoid (*N* = 18)	**Gliptin-associated BP (*N* = 1)**	**Classical BP and non-bullous pemphigoid (*N* = 32)**	**Immunotherapy-associated BP (*N* = 3)**	**Gliptin-associated BP (*N* = 4)**	**Total (*N* = 58)**
Time of hospitalization[c] (weeks)						
N	2	0	1	1	1	5
Mean (SD)	2 (1.4)	—	2 (–)	2 (–)	2 (–)	2 (0.71)
Median (IQR)	2 (1.5, 3)	—	2 (2, 2)	2 (2, 2)	2 (2, 2)	2 (2, 2.2)
No. of previous treatments[c]						
N	18	1	32	3	4	58
Mean (SD)	3.3 (1.8)	1.0 (.)	2.7 (1.2)	2.0 (1.00)	3.3 (0.50)	2.9 (1.4)
Median (IQR)	3.0 (2.0, 4.0)	1.0 (1.0, 1.0)	2.5 (2.0, 3.0)	2.0 (1.0, 3.0)	3.0 (3.0, 3.5)	3.0 (2.0, 3.0)
Previous treatments,[c] *n* (%)						
Systemic steroids	18 (100%)	1 (100%)	31 (96.9%)	3 (100%)	4 (100%)	57 (98.3%)
Topical steroids	12 (66.7%)	0 (0.0%)	17 (53.1%)	1 (33.3%)	4 (100%)	34 (58.6%)
Dapsone	7 (38.9%)	0 (0.0%)	7 (21.9%)	1 (33.3%)	1 (25.0%)	16 (27.6%)
Doxycycline	3 (16.7%)	0 (0.0%)	11 (34.4%)	0 (0%)	4 (100%)	18 (31.0%)
Methotrexate	6 (33.3%)	0 (0.0%)	8 (25.0%)	0 (0%)	0 (0%)	14 (24.1%)
Mycophenolate mofetil	4 (22.2%)	0 (0.0%)	2 (6.2%)	0 (0%)	1 (25.0%)	7 (12.1%)
Azathioprine	2 (11.1%)	0 (0.0%)	5 (15.6%)	0 (0%)	0 (0.0%)	7 (12.1%)
Cyclosporine	2 (11.1%)	0 (0.0%)	1 (3.1%)	0 (0%)	0 (0.0%)	3 (5.2%)
Rituximab	2 (11.1%)	0 (0.0%)	1 (3.1%)	0 (0%)	0 (0.0%)	3 (5.2%)
IVIG	1 (5.6%)	0 (0.0%)	0 (0.0%)	1 (33.3%)	0 (0.0%)	2 (3.5%)
Colchicine	1 (5.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.7%)
Nicotinamide	0 (0.0%)	0 (0.0%)	1 (3.1%)	0 (0.0%)	0 (0.0%)	1 (1.7%)

Abbreviations: BMI = body mass index, BP = bullous pemphigoid, DIF = direct immunofluorescence, F = female, Ig = Immunoglobulin, IIF = Indirect immunofluorescence, IQR = interquartile range, IVIG = intravenous dimmunoglobulin, M = male, *N* = number, SD = standard deviation.

[a]Defined as a non-bullous variant of BP, characterized by persistent, intensely pruritic urticarial plaques without initial blistering, often mimicking chronic urticaria and typically lacking mucosal involvement [2].

[b]IU/mL.

[c]Prior to introduction of dupilumab or omalizumab.

TABLE 2 | Baseline outcomes at the time of dupilumab or omalizumab introduction.

	Omalizumab		Dupilumab			
	Classical BP and non-bullous pemphigoid (*N* = 18)	**Gliptin-associated BP (*N* = 1)**	**Classical BP and non-bullous pemphigoid (*N* = 32)**	**Immunotherapy-associated BP (*N* = 3)**	**Gliptin-associated BP (*N* = 4)**	**Total (*N* = 58)**
BP duration[a] (months)						
N	18	1	32	3	4	58
Mean (SD)	29.3 (32.0)	3.0 (–)	21.0 (21.7)	13.0 (1.7)	15.0 (9.8)	22.5 (24.4)
Median (IQR)	18.0 (6.0, 48.0)	3.0 (3.0, 3.0)	12.0 (4.0, 30.0)	12.0 (12.0, 15.0)	12.5 (9.0, 21.0)	12.5 (5.75, 30.0)
Concomitant BP-specific therapy,[b] *n* (%)						
Yes	18 (100.0%)	1 (100.0%)	24 (75.0%)	2 (66.7%)	4 (100.0%)	49 (84.5%)
No	0 (0.0%)	0 (0.0%)	8 (25.0%)	1 (33.3%)	0 (0.0%)	9 (15.5%)
Concomitant BP-specific therapy, b*n* (%)						
Systemic steroids	16 (88.9%)	1 (100%)	19 (59.4%)	2 (66.7%)	4 (100%)	42 (72.4%)
Topical steroids	5 (27.8%)	0 (0.0%)	12 (37.5%)	0 (0.0%)	3 (75%)	20 (34.5%)
Dapsone	2 (11.1%)	0 (0.0%)	4 (12.5%)	1 (33.3%)	0 (0.0%)	7 (12.1%)
Doxycycline	1 (5.6%)	0 (0.0%)	1 (3.1%)	0 (0.0%)	2 (50%)	4 (6.9%)
Methotrexate	0 (0.0%)	0 (0.0%)	3 (9.4%)	0 (0.0%)	0 (0.0%)	3 (5.2%)
Mycophenolate mofetil	3 (16.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (5.2%)
Azathioprine	0 (0.0%)	0 (0.0%)	2 (6.3%)	0 (0.0%)	0 (0.0%)	2 (3.5%)
BPDAI baseline						
N	17	1	31	3	4	56
Mean (SD)	68.9 (41.18)	36.0 (.)	35.2 (28.8)	54.0 (19.7)	26.5 (19.9)	45.8 (35.2)
Median (IQR)	75.0 (40.0, 96.0)	36.0 (36.0, 36.0)	30.0 (15.0, 46.0)	60.0 (32.0, 70.0)	20.5 (13.0, 40.0)	39.0 (17.8, 58.8)
Serum anti-BP180 IgG baseline						
N	14	1	14	3	0	32
Mean (SD)	106.7 (74.4)	9.0 (.)	67.4 (52.9)	59.6 (41.2)	—	84.6 (64.2)
Median (IQR)	113.0 (60.8, 150.0)	9.0 (9.0, 9.0)	72.5 (18.8, 100.0)	48.1 (25.3, 105.3)	—	95 (22.0, 120.3)
Serum anti-BP230 IgG baseline						

(Continues)

TABLE 2 | (Continued)

	Omalizumab		Dupilumab			
	Classical BP and non-bullous pemphigoid (*N* = 18)	**Gliptin-associated BP (*N* = 1)**	**Classical BP and non-bullous pemphigoid (*N* = 32)**	**Immunotherapy-associated BP (*N* = 3)**	**Gliptin-associated BP (*N* = 4)**	**Total (*N* = 58)**
N	11	1	11	0	0	23
Mean (SD)	61.9 (58.2)	9.0 (.)	32.9 (46.4)	—	—	46.9 (53.8)
Median (IQR)	52.0 (13.0, 91.9)	9.0 (9.0, 9.0)	20.4 (2.9, 35.7)	—	—	28.7 (6.8, 69.3)
Serum anti-BP180 IgG baseline, *n* (%)						
Yes	11 (78.6%)	0 (0.0%)	12 (75.0%)	3 (100.0%)	0 (0.0%)	26 (76.5%)
No	3 (21.4%)	1 (100.0%)	4 (25.0%)	0 (0.0%)	0 (0.0%)	8 (23.5%)
Serum anti-BP230 IgG baseline, *n* (%)						
Yes	8 (66.7%)	0 (0.0%)	5 (35.7%)	0 (0.0%)	0 (0.0%)	13 (44.8%)
No	4 (33.3%)	1 (100.0%)	9 (64.3%)	2 (100.0%)	0 (0.0%)	16 (55.2%)
DLQI score baseline						
N	10	0	21	2	4	37
Mean (SD)	22.1 (6.6)	—	15.9 (5.2)	25.0 (7.0)	13.5 (5.0)	17.8 (6.4)
Median (IQR)	24.0 (16.0, 28.0)	—	15.0 (13.0, 20.0)	25.0 (20.0, 30.0)	12.5 (9.5, 17.5)	18.0 (13.0, 22.0)
PP-NRS score baseline						
N	15	3	28	2	2	50
Mean (SD)	6.5 (2.8)	—	8.6 (1.2)	8.5 (0.7)	6.0 (.)	7.8 (2.0)
Median (IQR)	8.0 (3.5, 8.3)	—	9.0 (7.8, 9.3)	8.5 (8.0, 9.0)	6.0 (6.0, 6.0)	8.0 (7.0, 9.0)
Serum IgE levels at baseline (IU/mL)						
N	14	0	20	1	1	36
Mean (SD)	1149.1 (1348.41)	—	731.1 (941.27)	1550.0 (.)	56.0 (.)	913.2 (1101.0)
Median (IQR)	521.0 (312.0, 1638.0)	—	408.0 (181.0, 787.0)	1550.0 (1550.0, 1550.0)	56.0 (56.0, 56.0)	494.5 (222.0, 1346.0)
Concomitant malignancy,[b] *n* (%)						
Yes	2 (11.1%)	0 (0.0%)	2 (6.5%)	3 (100.0%)	0 (0.0%)	7 (12.3%)

(Continues)

TABLE 2 | (Continued)

	Omalizumab		Dupilumab			
	Classical BP and non-bullous pemphigoid ($N=18$)	Gliptin-associated BP ($N=1$)	Classical BP and non-bullous pemphigoid ($N=32$)	Immunotherapy-associated BP ($N=3$)	Gliptin-associated BP ($N=4$)	Total ($N=58$)
No	16 (88.9%)	1 (100.0%)	29 (93.5%)	0 (0.0%)	4 (100.0%)	50 (87.7%)
Hospitalization for BP,[b] *n* (%)						
Yes	2 (11.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (3.6%)
No	15 (88.2%)	1 (100.0%)	31 (100.0%)	3 (100.0%)	4 (100.0%)	54 (96.4%)
Duration of hospitalization for BP						
N	9	0	11	1	3	24
Mean (SD)	0.7 (1.41)	—	0.0 (0.00)	7.0 (.)	0.0 (0.00)	0.5 (1.64)
Median (IQR)	0.0 (0.0, 0.0)	—	0.0 (0.0, 0.0)	7.0 (7.0, 7.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)

Abbreviations: BP = bullous pemphigoid, BPDAI = bullous pemphigoid disease area index, DLQI = dermatology life quality index, Ig = immunoglobulin, IQR = interquartile range, *N* = number, PP-NRS = peak pruritus numeric rating scale, SD = standard deviation.

[a]Prior to introduction of dupilumab or omalizumab.

[b]At dupilumab or omalizumab baseline.

half of the patients ($n=5/14$; 35.7%), following a mean time of 7.3 ± 5.1 months. Overall, 11/18 patients (61.1%) discontinued the drug: Five due to treatment ineffectiveness (45.4%), four because of clinical remission (36.3%), one was lost to follow-up (9%), and one according to CSU therapy protocol (9%). Data stratified by potential confounders (such as the BP type and the reason for the introduction of biologic therapy) are available in Tables S4 and S5.

3.3 | Outcomes Analyses

3.3.1 | Primary and Secondary Outcomes

Considering baseline characteristics, omalizumab-treated patients had a statistically significant higher BPDAI score and total cumulative prednisone dose compared to those treated with dupilumab (mean value of 68.9 ± 41.1 vs. 35.2 ± 28.8 [$p=0.005$] and 3672.6 ± 710 mg vs. 1041.0 ± 1816.9 [$p=0.005$], respectively for the two variables). No significant differences were observed in terms of concomitant therapies at any time point of interest between the two treatment groups (Table 4). Descriptively, dupilumab appeared to perform better in terms of disease control rate (at both 8 weeks and at the end of follow-up) and relapse incidences, but statistical analysis showed no significant differences (Figure 3). Specifically, dupilumab-treated and omalizumab-treated patients reached a rate of 56.2% versus 27.8% ($p=0.2709$), 90.6% versus 77.8% ($p=0.2089$), and 14.3% versus 35.7% ($p=0.1106$) for these three outcomes. In terms of treatment response, dupilumab again outperforms omalizumab descriptively, with 87.1% of subjects achieving complete response (considering both off therapy and on minimal therapies) compared to the 64.7% of patients treated with omalizumab. However, statistical tests showed no significant differences at all levels of response. Finally, parameter estimates associated with the fixed effect of time were consistently negative, suggesting that all scores tend to decrease over time for patients treated with both omalizumab and dupilumab. Except for the PP-NRS score in omalizumab-treated patients, all estimates result statistically significant (Table S3).

3.3.2 | Immunotherapy-Associated Bullous Pemphigoid

We observed three cases of immunotherapy-associated BP treated with dupilumab. Of these, 2/3 (66.6%) occurred following pembrolizumab administration for lung cancer and 1/3 (33.3%) following nivolumab for metastatic melanoma. In these cases, immunotherapy was either temporarily or permanently discontinued, except in one case where it was continued. These patients had a mean of 2.0 ± 1.0 prior treatments, with a mean disease duration of 13.0 ± 1.7 months. The primary reason for introducing dupilumab was the presence of comorbidities that contraindicated the use of corticosteroids and immunosuppressants ($n=3/3$; 100%). Additionally, 2/3 (66.6%) showed resistance to previous treatments, and one patient (33.3%) had a concurrent diagnosis of AD. During a mean follow-up period of 9.3 ± 6.3 months, 2/3 (66.6%) received oral corticosteroids (OCS). All patients achieved disease control, respectively within 4, 20, and 24 weeks following the introduction of dupilumab, with a mean of 16.0 ± 10.5 weeks. Complete remission was achieved in

TABLE 3 | Treatment outcomes with dupilumab or omalizumab throughout the study period.

	Omalizumab		Dupilumab			
	Classical BP and non-bullous pemphigoid (*N* = 18)	Gliptin-associated BP (*N* = 1)	Classical BP and non-bullous pemphigoid (*N* = 32)	Immunotherapy-associated BP (*N* = 3)	Gliptin-associated BP (*N* = 4)	Total (*N* = 58)
Concomitant BP-specific therapy[a]						
N	18	1	31	3	3	56
Mean (SD)	2.1 (0.8)	1.0 (.)	1.2 (0.8)	0.7 (0.5)	2.0 (0.00)	1.5 (0.9)
Median (IQR)	2.0 (1.0, 3.0)	1.0 (1.0, 1.0)	1.0 (0.0, 2.0)	1.0 (0.0, 1.0)	2.0 (2.0, 2.0)	1.5 (1.0, 2.0)
Concomitant BP-specific therapy,[a] *n* (%)						
Systemic steroids	15 (83.3%)	1 (100%)	19 (59.4%)	2 (66.7%)	3 (75%)	40 (68.9%)
Topical steroids	12 (66.7%)	0 (0.0%)	8 (25%)	0 (0.0%)	2 (50%)	22 (37.9%)
Dapsone	3 (16.7%)	0 (0.0%)	1 (3.1%)	0 (0.0%)	0 (0.0%)	4 (6.9%)
Doxycycline	1 (5.6%)	0 (0.0%)	2 (6.3%)	0 (0.0%)	1 (25%)	4 (6.9%)
Mycophenolate mofetil	4 (22.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (6.9%)
Azathioprine	0 (0.0%)	0 (0.0%)	2 (6.3%)	0 (0.0%)	0 (0.0%)	2 (3.5%)
Methotrexate	1 (5.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.7%)
Follow-up duration (months)						
N	17	1	32	3	3	56
Mean (SD)	19.8 (10.7)	2.0 (.)	9.7 (6.4)	9.3 (6.3)	8.0 (3.00)	12.5 (9.1)
Median (IQR)	18.0 (12.0, 24.0)	2.0 (2.0, 2.0)	9.0 (4.0, 13.5)	13.0 (2.0, 13.0)	8.0 (5.0, 11.0)	11.5 (5.0, 17.3)
Disease control achieved, *n* (%)						
Yes	14 (77.8%)	0 (0.0%)	29 (90.6%)	3 (100.0%)	3 (100.0%)	49 (86.0%)
No	4 (22.2%)	1 (100.0%)	3 (9.4%)	0 (0.0%)	0 (0.0%)	8 (14.0%)
Time to achieve disease control (weeks)						
N	14	0	28	3	3	48
Mean (SD)	11.6 (6.70)	—	9.3 (5.0)	16.0 (10.6)	8.0 (4.00)	10.3 (6.0)
Median (IQR)	10.5 (8.0, 14.0)	—	8.0 (6.0, 10.5)	20.0 (4.0, 24.0)	8.0 (4.0, 12.0)	8.0 (6.3, 12.0)
Concomitant BP-specific therapy[b]						
N	14	0	22	2	3	41
Mean (SD)	1.3 (0.8)	—	1.0 (0.4)	1.0 (0.00)	1.0 (0.00)	1.1 (0.60)
Median (IQR)	1.0 (1.0, 2.0)	—	1.0 (1.0, 1.0)	1.0 (1.0, 1.0)	1.0 (1.0, 1.0)	1.0 (1.0, 1.0)
Concomitant BP-specific therapy,[b] *n* (%)						
Systemic steroids	11 (61.1%)	0 (0%)	18 (56.3%)	2 (66.7%)	3 (75%)	34 (58.6%)
Topical steroids	2 (11.1%)	0 (0%)	3 (9.4%)	0 (0%)	0 (0%)	5 (8.6%)
Dapsone	2 (11.1%)	0 (0%)	1 (3.1%)	0 (0%)	0 (0%)	3 (5.2%)

(Continues)

TABLE 3 | (Continued)

	Omalizumab		Dupilumab			
	Classical BP and non-bullous pemphigoid (*N* = 18)	**Gliptin-associated BP (*N* = 1)**	**Classical BP and non-bullous pemphigoid (*N* = 32)**	**Immunotherapy-associated BP (*N* = 3)**	**Gliptin-associated BP (*N* = 4)**	**Total (*N* = 58)**
Mycophenolate mofetil	2 (11.1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (3.5%)
Azathioprine	0 (0%)	0 (0%)	1 (3.1%)	0 (0%)	0 (0%)	1 (1.7%)
Doxycycline	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0.0%)
Methotrexate	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0.0%)
Treatment response,[c] *n* (%)						
Complete remission on minimal therapy	11 (64.7%)	0 (0.0%)	22 (71.0%)	1 (33.3%)	3 (100.0%)	37 (63.8%)
Complete remission off therapy	0 (0.0%)	0 (0.0%)	5 (16.1%)	1 (33.3%)	0 (0.0%)	6 (10.3%)
Partial remission on minimal therapy	3 (17.6%)	0 (0.0%)	1 (3.2%)	1 (33.3%)	0 (0.0%)	5 (8.6%)
Partial remission off therapy	0 (0.0%)	0 (0.0%)	1 (3.2%)	0 (0.0%)	0 (0.0%)	1 (1.7%)
Stable disease	3 (17.6%)	0 (0.0%)	1 (3.2%)	0 (0.0%)	0 (0.0%)	4 (6.9%)
Progressive disease	0 (0.0%)	0 (0.0%)	1 (3.2%)	0 (0.0%)	0 (0.0%)	1 (1.7%)
Concomitant BP-specific therapy[d]						
N	14	0	18	2	3	37
Mean (SD)	1.3 (0.8)	—	1.1 (0.4)	1.0 (–)	1.0 (–)	1.1 (0.6)
Median (IQR)	1.0 (1.0, 2.0)	—	1.0 (1.0, 1.0)	1.0 (1.0, 1.0)	1.0 (1.0, 1.0)	1.0 (1.0, 1.0)
Concomitant BP-specific therapy,[d] *n* (%)						
Systemic steroids	11 (61.1%)	0 (0%)	15 (46.9%)	2 (66.7%)	3 (75%)	31 (53.5%)
Topical steroids	1 (5.6%)	0 (0%)	3 (9.4%)	0 (0%)	0 (0%)	4 (6.9%)
Dapsone	2 (11.1%)	0 (0%)	1 (3.1%)	0 (0%)	0 (0%)	3 (5.2%)
Mycophenolate mofetil	3 (16.7%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	3 (5.2%)
Doxycycline	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0.0%)
Methotrexate	1 (5.6%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (1.7%)
Cumulative prednisone dose[e] (mg)						
N	17	1	29	3	4	54

(Continues)

TABLE 3 | (Continued)

	Omalizumab		Dupilumab			
	Classical BP and non-bullous pemphigoid (*N* = 18)	Gliptin-associated BP (*N* = 1)	Classical BP and non-bullous pemphigoid (*N* = 32)	Immunotherapy-associated BP (*N* = 3)	Gliptin-associated BP (*N* = 4)	Total (*N* = 58)
Mean (SD)	3672.6 (3710.1)	375.0 (–)	1041.0 (1816.9)	374.1 (324.0)	887.5 (556.2)	2399.9 (2530.7)
Median (IQR)	3500.0 (750.0, 5050.0)	375.0 (375.0, 375.0)	560.0 (0.0, 1060.0)	560 (0.0, 62.5)	787.5 (487.5, 1187.5)	600 (225.0, 1628.0)
Time to complete remission (months)						
N	7	0	25	3	3	38
Mean (SD)	9.6 (7.9)	—	4.9 (5.7)	1.0 (1.00)	3.7 (3.7)	5.4 (6.2)
Median (IQR)	11.0 (2.5, 13.0)	—	3.0 (2.0, 5.0)	1.0 (0.0, 2.0)	2.0 (1.0, 8.0)	3.0 (2.0, 7.0)
BP relapse, *n* (%)						
Yes	5 (35.7%)	0 (0.0%)	3 (10.3%)	0 (0.0%)	0 (0.0%)	8 (17.0%)
No	9 (64.3%)	0 (0.0%)	26 (89.7%)	3 (100.0%)	3 (100.0%)	41 (87.2%)
Time to relapse (months)						
N	3	0	4	0	0	7
Mean (SD)	7.3 (5.1)	—	5.3 (4.0)	—	—	6.3 (4.1)
Median (IQR)	6.0 (3.0, 13.0)	—	5.0 (2.0, 8.5)	—	—	6.0 (3.0, 10.0)

Abbreviations: BP = bullous pemphigoid, IQR = interquartile range, *N* = number, SD = standard deviation.
[a]Throughout the study period.
[b]At disease control.
[c]Complete remission on minimal therapy = absence of new or established lesions or pruritus while patient is receiving minimal therapy for at least 2 months, complete remission off therapy = absence of new or established lesions or pruritus while patient is off all BP therapy for at least 2 months, partial remission on minimal therapy = presence of transient new lesions that heal within 1 week while patient is receiving minimal therapy for at least 2 months, partial remission off therapy = presence of transient new lesions that heal within 1 week without treatment while patient is off all BP therapy for at least 2 months, minimal therapy = ≤ 0.1 mg/kg/day of prednisone (or equivalent) or 20 g/week of clobetasol propionate and/or minimal adjuvant or maintenance therapy, minimal adjuvant therapy and/or maintenance therapy = following doses or less: methotrexate 5 mg/week; azathioprine 0.7 mg/kg/day; mycophenolate mofetil 500 mg/day; mycophenolic acid 360 mg/day; or dapsone 50 mg/day.
[d]At treatment response.
[e]Calculated from the introduction of dupilumab or omalizumab for the entire study period.

2/3 (66.6%) of patients, with one on minimal therapy and the other off therapy, while one patient (33.3%) achieved partial remission on minimal therapy. No dupilumab discontinuation was recorded, and no AEs were observed. All patients remained relapse-free at the end of the study period.

3.3.3 | Gliptin-Associated Bullous Pemphigoid

Five patients were diagnosed with gliptin-associated bullous pemphigoid (BP) attributed to the use of DPP-4 inhibitors for the management of diabetes. Of these cases, 4/5 (80%) were treated with dupilumab: 1/4 (25%) associated with sitagliptin, 2/4 (50%) with linagliptin, and 1/4 (25%) with alogliptin. One case associated with the use of linagliptin was treated with omalizumab. Dupilumab-treated subjects had previously undergone a mean of 3.3 ± 0.5 different treatments, with a mean disease duration of 15.0 ± 9.8 months. All initiated the drug because of resistance to previous treatments and the presence of comorbidities that contraindicated the use of corticosteroids and immunosuppressants. Following the administration of dupilumab, all patients achieved disease control, with a mean time to disease control of 16.0 ± 10.58 weeks. All patients reached complete remission on minimal therapy using systemic steroids, with only 1/4 (25%) discontinuing dupilumab due to adverse events. In contrast, the patient who received omalizumab had a disease duration of 3 months and was undergoing ineffective systemic steroid therapy. Omalizumab was introduced but discontinued after 8 weeks due to failure to achieve disease control.

3.4 | Safety Outcomes

Within the group undergoing dupilumab therapy, AEs were found in 2/39 patients (5.1%): One case of concurrent arthralgia and myalgia and one case of alopecia areata, which led to the discontinuation of the drug. In the omalizumab group, no AEs were reported.

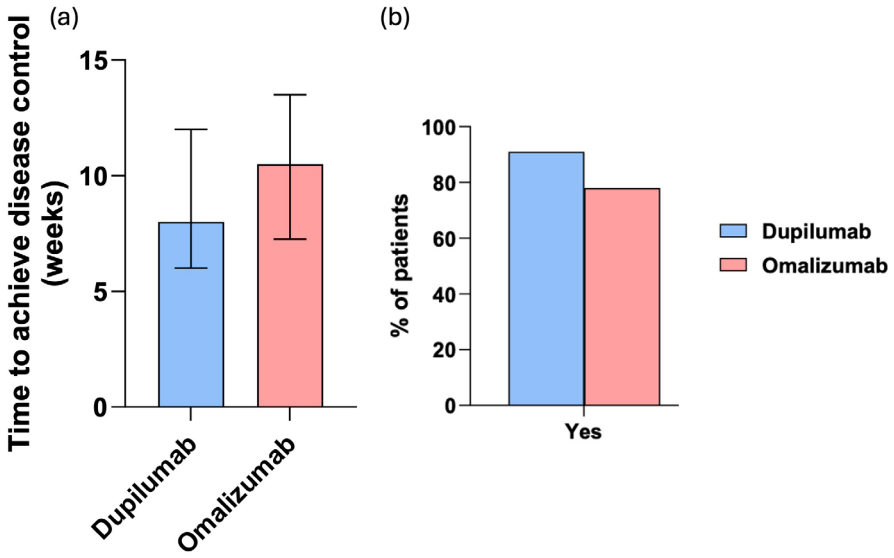

FIGURE 1 | (a) Bar graph showing the median time to achieve disease control in weeks for patients treated with dupilumab (blue) and omalizumab (red). Dupilumab-treated patients achieved disease control in a mean of approximately 8 weeks, whereas omalizumab-treated patients achieved disease control in an average of approximately 10 weeks. (b) Bar graph showing the percentage of patients who achieved disease control with dupilumab and omalizumab. A higher percentage of patients treated with dupilumab (around 90%) achieved disease control compared to those treated with omalizumab (approximately 80%).

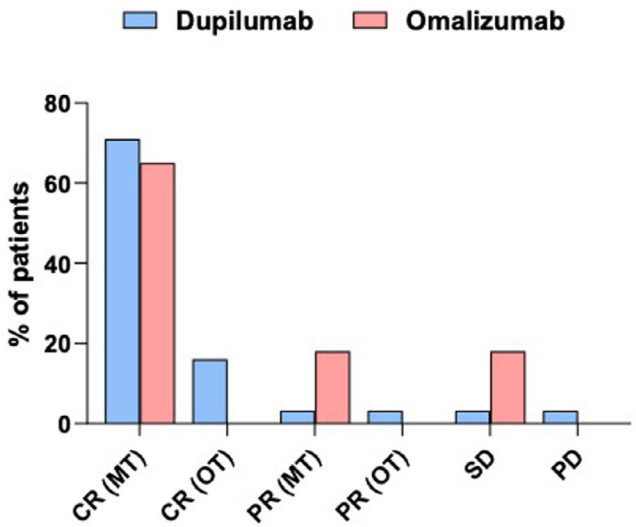

FIGURE 2 | Bar graph showing the percentage of patients achieving different pattern of response to treatment with dupilumab and omalizumab. CR (MT) = complete remission on minimal therapy, CR (OT) = complete remission off therapy, PR (MT) = partial remission on minimal therapy, PR (OT) = partial remission off therapy, SD = stable disease, PD = progressive disease.

4 | Discussion

The primary reason for this study was to address the lack of information concerning the use of biological agents in BP by providing real-life data relating to their routine use in Italy. The treatment patterns observed reflect the clinical practices and preferences of physicians regarding the utilization of dupilumab or omalizumab in a substantial and representative sample across the country. In clinical practice, the duration of OCS therapy is a key factor, as prolonged use is associated with increased toxicity and higher mortality, particularly in elderly patients [1]. Although the optimal duration of OCS therapy remains uncertain, expert recommendations suggest a total treatment period of 4–12 months [30]. However, real-world data indicate that continuous OCS use often extends well beyond these recommendations [31].

There were no significant differences between the dupilumab and omalizumab group in terms of BP disease duration and concomitant therapies at baseline. However, the BPDAI scores were higher in the omalizumab group, indicating more severe disease at baseline. It is possible that the higher cumulative dose of prednisone received by patients treated with omalizumab might have mitigated the impact of the higher BPDAI scores on our exploratory analyses. While dupilumab showed a trend toward faster disease control and higher clinical remission compared to omalizumab, these differences were not statistically significant, which could be attributed to the small sample size.

Our results align with previous reports suggesting a favorable safety and effective profile for both biologics, both in BP [6–20] and in other autoimmune bullous disorders [32–39]. The improvements observed through inhibition of the Th2 pathway and IgE are consistent with their proposed roles in BP pathogenesis [40–45].

In this study, inferential analyses were exclusively conducted on classical BP and non-bullous pemphigoid cases. This methodology was adopted to minimize the potential confounding effect of underlying biological differences between BP and drug-associated BP, whose low representation in our cohort precluded reliable inferential conclusions. However, these entities were descriptively evaluated to provide an assessment of the effectiveness of these drugs in subsets of patients where real-world data are scarce and have been excluded from the only ongoing phase 2/3 randomized controlled trial LIBERTY-BP ADEPT [28]. Furthermore, to address potential confounders, effectiveness outcomes have been stratified according to

TABLE 4 | Statistical analysis for baseline characteristics and exploratory outcomes (classic BP and non-bullous pemphigoid only).

	Omalizumab ($N=18$)	Dupilumab ($N=32$)	Total ($N=50$)	p
Baseline characteristics				
BPDAI baseline				
N	17	31	48	0.00573[h]
Mean (SD)	68.9 (41.1)	35.2 (28.8)	47.1 (37.0)	
Median (IQR)	75.0 (40.0, 96.0)	30.0 (15.0, 46.0)	40.5 (19.0, 57.5)	
BP duration[a] (months)				
N	18	32	50	
Mean (SD)	29.3 (32.0)	21.0 (21.7)	24.0 (25.9)	0.46023[h]
Median (IQR)	18.0 (6.0, 48.0)	12.0 (4.0, 30.0)	14.0 (5.0, 31.0)	
Cumulative prednisone dose[b] (mg)				
N	17	29	46	
Mean (SD)	3672.6 (3710.1)	1041.0 (1816.9)	2013.6 (2932.2)	0.00531[h]
Median (IQR)	3500.0 (750.0, 5050.0)	560.0 (0.0, 1060.0)	825.0 (69.0, 2895.0)	
Concomitant BP-specific therapy,[c] *n* (%)				
Any treatment	18 (100.0%)	24 (75.0%)	42 (84.0%)	0.0206[g]
Topical steroids	5 (27.8%)	12 (41.4%)	17 (36.2%)	0.3455[g]
Systemic steroids	16 (88.9%)	19 (65.5%)	35 (74.5%)	0.0741[g]
Mycophenolate mofetil	3 (16.7%)	0 (0.0%)	3 (6.4%)	0.0231[g]
Doxycycline	1 (5.6%)	1 (3.4%)	2 (4.3%)	0.7279[g]
Azathioprine	0 (0.0%)	2 (6.9%)	2 (4.3%)	0.2548[g]
Dapsone	2 (11.1%)	4 (13.8%)	6 (12.8%)	0.7888[g]
Methotrexate	0 (0.0%)	3 (9.7%)	3 (6.1%)	0.1731[g]
Disease control rate				
Disease control rate, *n* (%)				
At 8 weeks	5 (27.8%)	18 (56.3%)	23 (46.0%)	0.2709[g]
At the end of follow-up	14 (77.8%)	29 (90.6%)	43 (86.0%)	0.2089[g]
Event rate (95% CI)	0.2 (0.0–0.4)	0.1 (0.0–0.2)	0.1 (0.0–0.2)	
Odds ratio (95% CI)	2.8 (0.5–14.1)	Reference		0.2211[f]
Concomitant BP-specific therapy[d]				
Any treatment	14 (100.0%)	22 (100.0%)	36 (100.0%)	NA
Topical steroids	2 (14.3%)	3 (13.6%)	5 (13.9%)	0.9562[g]
Systemic steroids	11 (78.6%)	18 (81.8%)	29 (80.6%)	0.8104[g]
Dapsone	2 (14.3%)	1 (4.5%)	3 (8.3%)	0.3026[g]
Mycophenolate mofetil	2 (14.3%)	0 (0.0%)	2 (5.6%)	0.0681[g]
Doxycycline	0 (0.0%)	0 (0.0%)	0 (0.0%)	NA
Methotrexate	0 (0.0%)	0 (0.0%)	0 (0.0%)	NA
Azathioprine	0 (0.0%)	1 (4.3%)	1 (2.7%)	0.4290[g]

(Continues)

TABLE 4 | (Continued)

	Omalizumab (*N* = 18)	Dupilumab (*N* = 32)	Total (*N* = 50)	*p*
Relapse after disease control achieved				
Months				
Events/*N*	5/14	4/28[i]	9/42	
Median (95% CI)	33.22 (21.39 - NE)	NE (NE - NE)	33.22 (33.22 - NE)	0.11062[h]
Hazard ratio (95% CI)	Reference	0.71 (0.17–2.93)		
Wald *p*-value	Reference	0.6361[f]		
Treatment response				
Treatment response, *n* (%)				
Complete remission on minimal therapy	11 (64.7%)	22 (71.0%)	33 (66%)	0.6547[g]
Complete remission off therapy	0 (0.0%)	5 (16.1%)	5 (10%)	0.0802[g]
Partial remission on minimal therapy	3 (17.6%)	1 (3.2%)	4 (8%)	0.0838[g]
Partial remission off therapy	0 (0.0%)	1 (3.2%)	1 (2%)	0.4543[g]
Stable disease	3 (17.6%)	1 (3.2%)	4 (8%)	0.0838[g]
Progressive disease	0 (0.0%)	1 (3.2%)	1 (2%)	0.4543[g]
No. of concomitant BP-specific therapy[e]				
N	14	18	32	
Mean (SD)	1.3 (0.8)	1.1 (0.4)	1.2 (0.6)	0.34083[h]
Median (IQR)	1.0 (1.0, 2.0)	1.0 (1.0, 1.0)	1.0 (1.0, 1.0)	
Concomitant therapies at the time treatment response was reached, *n* (%)				
Any treatment	14 (100.0%)	18 (100.0%)	32 (100.0%)	NA
Topical steroids	1 (7.1%)	3 (16.7%)	4 (12.5%)	0.4190[g]
Systemic steroids	11 (78.6%)	15 (83.3%)	26 (81.3%)	0.7321[g]
Mycophenolate mofetil	3 (21.4%)	0 (0.0%)	3 (9.4%)	0.0391[g]
Dapsone	2 (14.3%)	1 (5.6%)	3 (9.4%)	0.4006[g]
Methotrexate	1 (7.1%)	0 (0.0%)	1 (3.1%)	0.2493[g]
Doxycycline	0 (0.0%)	0 (0.0%)	0 (0.0%)	NA

Abbreviations: BP = bullous pemphigoid, BPDAI = bullous pemphigoid disease area index, CI = confidence interval, IQR = interquartile range, *N* = number, OCS = oral corticosteroid, SD = standard deviation.
[a]Prior to introduction of dupilumab or omalizumab.
[b]Calculated from the introduction of dupilumab or omalizumab for the entire study period.
[c]At dupilumab or omalizumab baseline.
[d]At disease control achieved.
[e]At the time treatment response was achieved.
[f]Type-3 Wald *p*-value.
[g]Chi-squared *p*-value.
[h]Kruskal–Wallis *p*-value.
[i]One subject who reached DCR was excluded from relapse analysis due to missing relapse information.

BP subtype and the underlying reason for initiating biologic therapy. Patients receiving biologics for concomitant conditions with approved indications, or due to comorbidities contraindicating standard immunosuppressive or prolonged corticosteroid therapy, showed slightly better clinical outcomes compared to those initiated on biologics following resistance to previous treatments. Nevertheless, biologics demonstrated effectiveness regardless of the reason for their initiation. These findings suggest that the clinical reason for initiating biologic treatment may influence therapeutic outcomes and should be carefully considered in clinical practice when planning management strategies for BP.

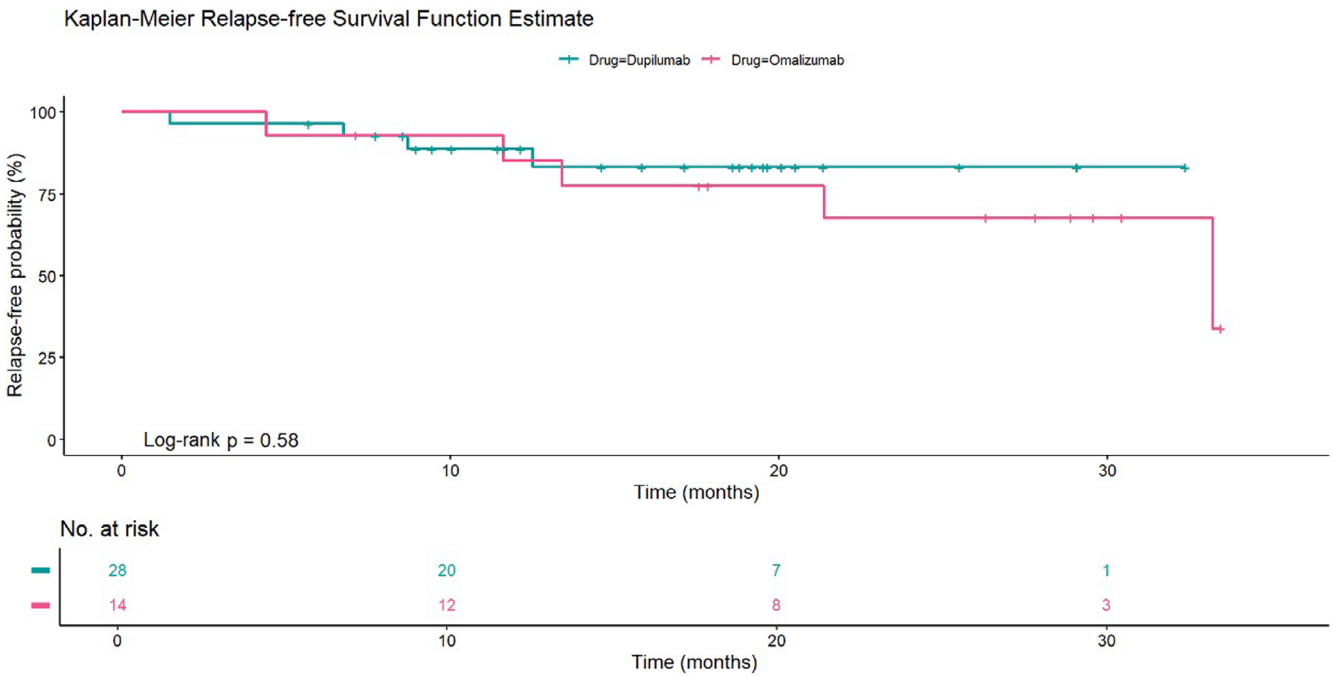

FIGURE 3 | Kaplan–Meier curve depicting the relapse-free survival estimates and the number of patients at risk for the two different treatments over a 30-month period. In the initial months, the Kaplan–Meier curves for both groups exhibit similar probability values, frequently intersecting and overlapping. Over time, the dupilumab group demonstrates a slightly but consistently higher relapse-free survival probability. Nevertheless, the overall plot suggests comparable survival experiences between the groups, consistent with the non-significant log-rank test $p = 0.5527$.

In our cohort, standard dosages of dupilumab and omalizumab were consistently administered to all but one patient. This uniform approach enhances the comparability of our groups as well as clarity in assessing treatment effects, differing from several studies where dosages were adjusted and not consistently equal among patients [10, 12, 14, 16]. The low incidence of serious AEs underscores the safety of these biologics in treating BP, aligning with their profiles in other dermatological conditions [46, 47].

5 | Limitations

Study limitations include the retrospective setting and the relatively small sample population of patients receiving either dupilumab or omalizumab. Nonetheless, our study assessed one of the largest cohorts reported to date. Notably, our sample consists entirely of Caucasian patients, potentially limiting the generalizability of our findings. However, it also constitutes a considerable cohort of Caucasian patients diagnosed with BP treated with dupilumab, as the majority of available data so far originates from investigations predominantly focused on populations of Asian descent [14]. Presence of IgE deposits in DIF was not tested, due to the lack of the respective assay at various centers for routine diagnostic purposes. Finally, the lack of a washout period as well as the absence of restriction on concomitant treatment in the study design may introduce bias, albeit reflecting clinical practice.

6 | Conclusions

This cohort of patients undergoing dupilumab or omalizumab adds to the existing evidence concerning the effectiveness of biologic agents in BP. Both biologics seems to be promising treatment adjuvants in the management of BP, with dupilumab showing a descriptive trend toward better outcomes. Further research, including larger and more heterogeneous populations, is warranted to validate these findings and explore the long-term effects of these treatments.

Ethics Statement

Reviewed and approved by the Institutional Review Board; approval #82821.

Consent

The patients described in this paper have given their written informed consent to the publication of their case details.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data supporting the findings of this study are available on request from the corresponding author.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.