SHORT COMMUNICATION

Combination of Omalizumab and Dupilumab for the Treatment of Severe Bullous Pemphigoid: a Series of 6 Cases

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Bullous pemphigoid (BP) is the most common autoimmune blistering dermatosis, typically affecting elderly individuals (1). Its incidence is rising (2). The mortality rate of BP patients is more than 3 times higher than that of the general population of the same age and sex (3). This is mainly explained by associated comorbidities and by the side effects of immunosuppressive treatments used in severe BP (1). According to the 2022 European guidelines for the management of BP, superpotent topical corticosteroids (CS) and systemic CS remain first-line treatments for severe cases (2). In CS-dependent or treatment-recalcitrant forms, several options are possible, including conventional immunosuppressants (azathioprine, methotrexate, mycophenolate mofetil), antibiotics with anti-inflammatory properties (doxycycline, dapsone), or biologics (omalizumab, dupilumab) (2). Omalizumab is a high-affinity monoclonal antibody targeting the Cε3 domain of IgE, leading to a decrease in total IgE serum levels and blood eosinophilia. Numerous case reports have shown that omalizumab can effectively reduce the severity of BP (4). The use of omalizumab may allow for CS-sparing and is well tolerated (5, 6). Dupilumab is a fully human monoclonal antibody that binds to the alpha subunit of the IL-4 receptor, shared by IL-4 and IL-13. It targets key mechanisms in Th2-mediated inflammatory diseases (7). BP patients receiving dupilumab in combination with conventional therapies have a faster clinical response and a reduction in the cumulative dose of systemic CS compared with those treated with conventional therapies alone (8, 9). While the efficacy of these 2 biologics used individually has been extensively reported, the combined use of omalizumab and dupilumab has only been documented in a single patient (10). Here, we report a series of 6 BP patients treated with the combination of omalizumab and dupilumab.

MATERIALS, METHODS AND RESULTS

Between 1 January 2017 and 30 June 2023, among 200 patients with BP seen in our department at Limoges university hospital, we treated 41 BP patients with biologics (including dupilumab or omalizumab) in addition to superpotent CS, doxycycline, or methotrexate. Among these, 6 patients were treated using a combination of omalizumab and dupilumab in addition to standard treatment. All 6 patients had severe and/or resistant disease with clinical features typical of BP, compatible skin histopathology, direct immunofluorescence (DIF) showing IgG and/or C3 deposits along the basement membrane, and consented to use of their medical data. Clinical data were retrospectively recorded from the hospital's electronic records and included demographic data (age, gender) and comorbidities, especially those representing a contraindication to conventional immunosuppressants. Disease-related data collected at diagnosis included: date of diagnosis (positive DIF), multi-bullous pattern (more than 10 new blisters daily), BPDAI score, serum levels of anti-BP180 and 230 autoantibodies (UR/mL) using ELISA kits (EUROIMMUN; Revvity Inc, Lübeck, Germany), serum total IgE levels (KU/L), maximum blood eosinophilia, and first-line treatments. Follow-up data included: BPDAI score, anti-BP180 and anti-BP230 autoantibody serum levels, blood eosinophilia, treatment modifications, adverse events, and occurrence of death according to Limoges hospital data or https://deces.matchid.io/search.

Table I summarizes the clinical and immunological characteristics at diagnosis of the 6 BP patients treated with dual biologic therapy and the details of their consecutive treatments. Among the 6 patients, 5 had contraindications to immunosuppressant initiation: 3 had a recent cancer, 1 had pulmonary sequelae from a past tuberculosis infection, and 1 developed acute tubular necrosis at the onset of the disease. The last patient (patient 1 in Table I) experienced acute renal failure 1 week after starting methotrexate for BP. Consequently, methotrexate was at once discontinued.

High-potent topical CS and doxycycline were started as first- and second-line treatments for all 6 patients. With the exception of patient 1 who received 1 methotrexate injection as third-line treatment and biologics as fourth- and fifth-line treatments, the other 5 patients received omalizumab as third-line and dupilumab as fourth-line treatment (see Table I). The average duration of the combined biologic therapy was 49 weeks (min. 18; max. 113). Dupilumab was added to omalizumab in all cases because BP was not in complete remission with omalizumab. The combination of both biologics led to regression of lesions in all 6 patients. However, discontinuation of the dual biologic therapy led to relapses in patient 3 (2 relapses) and patient 5 (1 relapse), requiring re-prescription of both treatments. Omalizumab was administered at a dose of 300 mg subcutaneously every 4 weeks, as for chronic idiopathic urticaria. This schedule was only increased to 300 mg every 2 weeks for the second relapse of patient 3. Dupilumab was administered at a dose of 600 mg subcutaneously, followed by 300 mg every 2 weeks. This dosage was never increased. Injection spacing was extended to 3 and 4 weeks for patients 1 and 3 before complete treatment discontinuation. No side effect attributable to these 2 biologics was reported. Patient 2 passed away while still receiving omalizumab. He developed pancytopenia and a SARS-CoV-2 infection after chemotherapy for a recurrence of squamous cell carcinoma.

DISCUSSION

We report the cases of 6 patients who received a combination of omalizumab and dupilumab for the treatment of their BP. While it is very well tolerated, this combination consistently led to complete remission of BP, although 2 patients experienced relapses after discontinuation of the combination. Before our series, this combination of

Table I. Clinical and immunological characteristics at diagnosis and treatment strategy of the 6 patients with bullous pemphigoid (BP) treated with dual biologic therapy

Factor	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Age[a]/Gender[b]	85, M	67, M	74, M	82, F	89, F	84, M
Triggering event	None	Immunotherapy	None	Immunotherapy	None	None
Contraindication to immunosuppressants at diagnosis	None	Cancer <5 years	Cancer <5 years and chronic kidney disease[c]	Cancer <5 years	None	COPD[d] and pulmonary sequelae of tuberculosis
Characteristics of BP[e]:						
More than 10 blisters/day	No	Yes	Not known	No	Yes	No
BPDAI[f]	Not known	72	22	28	112	29
Serum anti-BP180 Ab[g] UR/mL	< 2	200	< 2	> 200	> 200	> 200
Serum anti-BP230 Ab UR/mL	5	> 2	9	4	> 200	81
Total serum IgE[h] kU/L	61	Not known	25	52	3,937	2,780
Maximum EOS[i] G/L	0.6	0.8	0.2	1.0	3.5	0.2
Successive therapeutic lines	Week 0 [W0]: starting topical CS[j] W4: starting doxycycline W8: starting methotrexate W9: stopping methotrexate due to acute kidney failure Stopping doxycycline W10: starting omalizumab W26: addition of dupilumab W38: stopping topical CS W60: stopping omalizumab, maintaining dupilumab due to persistent itching until W130	W0: starting topical CS and doxycycline W1: starting omalizumab W8: addition of dupilumab W26: stopping dupilumab and topical CS W53: death of patient with ongoing omalizumab	W0: starting topical CS W4: starting doxycycline W23: starting omalizumab W30: addition of dupilumab W39: stopping dupilumab W47: relapse: restarting dupilumab W60: stopping topical CS W65: relapse: restarting topical CS W91: stopping doxycycline and topical CS W109: stopping dupilumab W132: relapse: restarting dupilumab and topical CS, omalizumab increased to 300 mg every 2 weeks	W0: starting topical CS W1: starting doxycycline W3: starting omalizumab W5: starting dupilumab W25: stopping topical CS W32: stopping dupilumab W104: stopping omalizumab due to clinical remission and antibody reduction W142: stopping doxycycline	W0: starting topical CS and doxycycline W7: starting omalizumab W16: addition of dupilumab W45: stopping topical CS W54: stopping dupilumab W94: restarting dupilumab and topical CS due to relapse W106: stopping omalizumab, dupilumab, and topical CS, continuing long-term doxycycline high antibodies	W0: starting topical CS W4: starting doxycycline W16: starting omalizumab W44: starting dupilumab due to BP flare W52: stopping topical CS W60: stopping doxycycline W96: stopping omalizumab W150: stopping dupilumab due to clinical remission and antibody reduction
Duration of omalizumab and dupilumab combination weeks	34	18	140[l]	28	50	52
Duration to complete disappearance weeks:						
Skin lesions	35	26	652	5	113	43
Itching	61	26	652	Not known	113	43

[a]Age at diagnosis, years; [b]sex, M: male; F: female; [c]stage IIIb; [d]chronic obstructive pulmonary disease; [e]at diagnosis; [f]Bullous Pemphigoid Disease Area Index; [g]antibody; [h]immunoglobulin E; [i]eosinophils; [j]corticosteroids; [k]week; [l]combination of dupilumab and omalizumab prescribed until early June 2025.

biologics had been reported only in a single case report (10): a 70-year-old patient with severe BP, resistant to corticosteroids, dapsone, methotrexate, and mycophenolate mofetil alone over 3 months, was successfully treated with dual omalizumab/dupilumab therapy combined with mycophenolate mofetil (10). In this case dupilumab was started 2 months after the initiation of omalizumab treatment (10). The 6 patients in our series did not receive immunosuppressants at the same time as the 2 biologics. However, they continue to receive the first-line treatment composed of topical CS plus doxycycline. Omalizumab was the first biologic therapy initiated. Dupilumab was added because BP was not in complete remission with omalizumab. The retrospective nature of our study did not allow for a precise assessment of the efficiency of each treatment on the evolution of anti-BP180 and anti-BP230 autoantibodies, total IgE levels, and eosinophil counts during treatment.

While European guidelines mention the possibility of using omalizumab or dupilumab for CS-resistant BP, there is currently no decision tree specifying which biologic to consider based on the patient's profile and disease characteristics. The influence of the posology of biologics has also been little studied. For omalizumab, Chebani et al. observed in a retrospective cohort of 100 patients that the final remission was not influenced by the omalizumab dosage. However, the time to remission was shorter for patients who received omalizumab at a higher dose than that used for chronic idiopathic urticaria (4). For dupilumab, the 2 largest published cohorts (Zhao et al. (8) and Planella-Fontanillas et al. (9)) have used the administration schemes for atopic dermatitis. The possibility of using higher doses of dupilumab to achieve faster remissions has not been published to date. This short series of 6 patients illustrates that the combination of omalizumab and dupilumab as add-on dual biologic therapy could be an alternative treatment strategy to immunosuppressants in severe and resistant BP, with a better benefit/risk. Nevertheless, prospective therapeutic studies are necessary to determine the optimal order of biologic therapy introduction and the optimal doses, and to more precisely define cases where the combination of both treatments may be beneficial.

The authors have no conflicts of interest to declare.

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