Dupilumab, an emerging therapeutic choice for recalcitrant subepidermal autoimmune bullous diseases: a case series of three patients

Subepidermal autoimmune bullous diseases (SABD) comprise a large group of chronic dermatoses, including namely (among others) bullous pemphigoid (BP), epidermolysis bullosa acquisita (EBA) and anti-p200 pemphigoid [1]. These diseases are characterized by the presence of autoantibodies that target distinct antigens of the basement membrane zone. Treatment of SABD is complex and different according to each particular disease. In BP, first-line therapy includes topical and systemic corticosteroids, while immunosuppressants are considered in resistant cases. However, these treatments can cause adverse events and pose additional risks in terms of COVID-19 [2]. A recent multicentre study suggested that dupilumab, an interleukin (IL)-4 receptor α-antagonist blocking IL-4 and IL-13 cytokine-induced responses, may be a novel therapy for BP [3]. The efficacy and safety of dupilumab in recalcitrant SABD remains to be further evaluated. We report three SABD cases with extensive lesions who did not respond to conventional therapies but improved after treatment with dupilumab.

All patients were diagnosed with SABD based on clinical manifestation, histology and direct immunofluorescence (supplementary table 1). The first patient had an inadequate response to various treatments, including systemic corticosteroids and immunosuppressive agents, and had multiple flares with corticosteroid tapering. She had a history of psychiatric disorder but had been in remission for eight years with no medication. During the last relapse (figure 1A, B), her disease progressed under a combined therapy of methylprednisolone (MEP) or dexamethasone (equivalent to 1.5-2.5 mg/kg/d prednisone), intravenous immunoglobulin (IVIG) and cyclophosphamide (CTX), and she suffered from mental and behavioural disorders. Dupilumab (600 mg) was administrated subcutaneously (SC), followed by 300 mg every other week for one month, in combination with prednisone at 0.75 mg/kg/d and CTX. The skin lesions improved rapidly within one week. After a month of dupilumab therapy, the patient’s disease had cleared. She was successfully tapered off prednisone over 12 weeks (figure 1C, D).

The second patient was diagnosed with BP considering serum positivity of anti-BP180 antibodies. He had a poor response to a combination of MEP (equivalent to 1.5-2.2 mg/kg/d prednisone), IVIG, methotrexate (MTX) and cyclosporine for three weeks (figure 1E, F). His HBsAg test was positive with high copies of HBV. Therefore, 600 mg dupilumab was added together with MEP, MTX and cyclosporine. The skin lesions were controlled with no new blisters within one week (figure 1G, H). Although dupilumab was discontinued due to cost, the patient showed

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**Figure 1.** Clinical presentation before and after dupilumab therapy. **A-D** Patient 1: extensive bullae and exudative and haemorrhagic crusts over the trunk, arms and legs (A, B); after four weeks of dupilumab therapy, bullae and crusting are absent and slight residual erythema on the trunk and pigmentation of the limbs are apparent (C, D). **E-H** Patient 2: tense bullae, haemorrhagic crusts and erythematous patches over the upper limbs and trunk (E, F); after two weeks of dupilumab therapy, bullae are absent, and erythema and milium over the hands, and pigmentation on the trunk and arms are apparent (G, H).
continuous improvement of skin lesions and pruritus, with prednisone tapering to 0.5 mg/kg/d over two months. In the third patient, conventional systemic therapies were undesirable due to underlying medical comorbidities. She discontinued prednisone due to active gastric ulcers and soon underwent a severe relapse of skin lesions with intense itch. Besides, her laboratory tests showed positive HBsAg with high copies of HBV. Considering all conditions, dupilumab treatment was introduced. Her pruritus greatly improved but not the skin lesions after three injections. No dupilumab-attributed adverse events were observed in these three patients.

Previously, most patients with BP received the dosing regimen approved for atopic dermatitis: 600 mg SC initially, followed by 300 mg SC every other week [3, 4]. We followed the same protocol here. Notably, our first and second patients were very treatment-resistant. During the most recent relapse, these patients did not respond to treatment with systemic corticosteroids at 0.5-0.75 mg/kg/d as an initial control and did not even respond when we gradually increased the dosage of corticosteroids with added immunosuppressants. Although these two patients were initially suspected to have BP, it is very unusual for BP to be unresponsive to all aggressive therapies. Thus, we could not completely exclude the possibility of other SABD such as BP-like EBA or anti-p200 pemphigoid, especially in the first case who in the absence of serological tests. Nevertheless, add-on dupilumab concomitant with conventional therapy in these two patients achieved rapid disease control with faster tapering of corticosteroids. To the best of our knowledge, the efficacy of dupilumab for such severe and recalcitrant conditions has only been reported twice in our knowledge, the efficacy of dupilumab for such severe and recalcitrant conditions has only been reported twice in patients with BP [5, 6]. Our three cases suggest a potential role of dupilumab in the treatment of refractory SABD. Further studies with larger sample sizes are needed to confirm these findings.

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Conflict of interest: none.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1684/ ejd.2021.4190. Table S1. Clinical summary of the three cases of recalcitrant subepidermal autoimmune bullous diseases (SABD).

Giant Bowen’s disease with unilateral verrucous epidermal nevus on non-sun-exposed skin

A 61-year-old man complained of the development of a pink-red scaly plaque on his left chest that had developed nearly three years ago. He had also suffered since childhood from keratotic plaques and papules on the left upper limb and the left chest. Examination of all systems was normal. Physical examination of the skin revealed a giant erosive plaque measuring 10 × 10 cm on the left chest, waxy skin-coloured scaly plaques on the edges of the rash, and linear verrucous plaques and papules on the left upper limb and left chest (figure 1A, B). Routine laboratory tests were normal. He was not taking medications and denied a family history of skin diseases, contact with chemical agents and a history of chronic wounds. Human papillomavirus (HPV) in the skin was negative. Superficial lymph nodes were normal, as shown by clinical and ultrasound examination. A biopsy from the plaque revealed hyperkeratosis, dyskeratosis, papillomatosis, loss of cell polarity, hyperchromatic nuclei, pleomorphism, atypical cells in the epidermis, koilicytic changes in the upper spinous layer and perivascular mononuclear cell infiltration in the papillary dermis (figure 1C-E). p53 staining was negative in the area affected by Bowen’s disease (figure 1F). According to the above findings, a diagnosis of unilateral verrucous epidermal nevus (VEN) and Bowen’s disease was made. The patient was treated with Mohs micrographic surgery and skin grafts from the thighs. VEN is a benign cutaneous hamartoma involving keratinocyte proliferation and is frequently seen in children. Clinically, VEN manifests with discrete, skin-coloured-to-brown, papillomatous papules or plaques [1]. Histologically, VEN is characterized by distinctive inflammatory and psoriasiform epidermal hyperplasia [2]. VEN is a benign hyperplasia of the epidermis, and is rarely associated with malignant tumours [3]. Nevertheless, epidermal nevus may be the origin of keratinocytic neoplasms such as keratoacanthoma, basal cell carcinoma, Bowen’s disease and cutaneous squamous cell carcinoma (CSCC) [4]. In the literature, most CSCC develop on linear or multiple VEN and rarely in solitary epidermal nevi [3]. The main pathomechanisms for the development of CSCC include exposure to physical agents such as UV light, chemical carcinogens, chronic wounds, HPV infection and scars.