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REVIEW

Strategies to Improve Outcomes of Bullous Pemphigoid: A Comprehensive Review of Clinical Presentations, Diagnosis, and Patients' Assessment

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Abstract: Bullous pemphigoid (BP) is the most frequent autoimmune bullous disease mainly affecting elderlies. Diagnosis usually results from clinical features, histological examination, and the quantification of circulating typical autoantibodies, due to its higher incidence in elderly patients, bullous pemphigoid treatment and management still represents a challenge due to the higher frequency of several comorbidities in this group of patients, which may also be linked to a reduced tolerance to BP treatments. Hence, an early diagnosis and a prompt correct treatment are mandatory to reach better clinical outcomes and improve as much as possible BP outcomes. Herein, we carried out a comprehensive literature review about the known clinical presentations, diagnosis, assessment and monitoring procedures used in daily clinical practice in patients with BP, to better define strategies to improve as much as possible BP clinical outcomes.

Keywords: bullous pemphigoid, pemphigoid, review, monitoring, assessment, prognosis

Introduction

Bullous pemphigoid (BP) is the most frequent autoimmune bullous disease mainly affecting elderlies.[1] It has been recently reported a notably increasing in incidence rates which may be related to the higher aging of population, drugs use, and increasing in diagnostic sensibility also in non-bullous presentations which were frequently underdiagnosed in the past.[2] Diagnosis usually results from clinical features, histological examination, and the quantification of circulating typical autoantibodies.[3] However, especially in the first phases of the disease, typical clinical features may be lacking, resulting in a late diagnosis and consequently treatment. Moreover, due to its higher incidence in elderly patients, BP treatment and management still represents a challenge due to the higher frequency of several comorbidities in this group of patients. Indeed, regarding BP prognosis, clinical risk factors linked to a higher mortality include older age, and neurological disorders with a higher incidence in elderly patients, such as dementia (including Alzheimer's disease). Furthermore, several comorbidities may also be linked to a reduced tolerance to BP treatments. Hence, an early diagnosis and a prompt correct treatment are mandatory to reach better clinical outcomes and improve as much as possible BP outcomes. Herein, we carried out a literature review about the known clinical features, diagnosis, assessment and monitoring procedures used in routine clinical practice in patients with BP, to better define strategies to improve as much as possible BP clinical outcomes.

Materials and Methods

A comprehensive review of the English-language medical literature was performed using PubMed, Ovid, Scopus, Embase, and Cochrane Library databases from their inception to 01 December 2021, using Medical Subject Headings (mesh) terms (if applicable) and medical terms for the concepts of BP diagnosis, treatment, assessment, management, and prognosis improvement. Search strategy to identify articles was performed using the following research terms: "bullous

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pemphigoid", "bullous", "bullous pemphigoid clinical features", "bullous pemphigoid management", "bullous pemphigoid assessment", "bullous pemphigoid management", bullous pemphigoid treatment", "bullous pemphigoid prognosis", and combinations thereof. Search involved all fields including title, abstract, keywords, and full text. Clinical and epidemiological studies, review and systematic review regarding BP diagnosis, assessment, and management were included. Papers published from the start of time through December 2021 and from all origins were considered. Therapies and management strategies that could be categorized as traditional Chinese medicine, herbal medicine or Ayurveda/Ayurvedic medicine have been excluded. The article is based on previously conducted studies.

Clinical Features

The BP clinical presentation can be highly variable, especially in the early stages of the disease or in atypical variations that lack the usual blistering lesions.[4,5] First signs and symptoms in the non-bullous phase, are commonly nonspecific, usually presenting with pruritus alone or accompanied by several types of lesions, including papular, urticarial, and eczematous lesions: these non-specific manifestations results in a difficult diagnosis. Moreover, this non-specific stage may last from just few days to several months and in some cases, pruritus is the sole indicator of BP.[6,7] The development of more typical vesicles and bullae is the main characteristic of the bullous stage of BP: in classic BP tense bullae, varying from 1 to 3 cm of diameter, and usually appearing on erythematous or normal skin.[8] Blisters turn into degraded, crusty areas which commonly heal without leaving scars. Milia, hyper- or hypopigmentation, and other post-inflammatory alterations may occur at this stage. The flexor surfaces upper and lower limbs, lower abdomen, and axillae are among the most involved sites.[9] The involvement of the mucosae may be verified in only 10–30% of individuals, with oral mucosae being the most frequently involved site,[4,5,10,11] while very rarely, nasal, conjunctival, pharyngeal, esophageal, and anogenital mucosae have been reported. BP typically presents with a chronic-remitting course, being self-limited in a few years. Although skin or mucosal lesions are rarely fatal, patients have a six-fold greater death rate than a healthy, age-matched population.[12]

Non-Bullous Cutaneous Pemphigoid

Typical bullae do not appear in many cases, and the early non-specific lesions, as indicated above, may represent the only sign of BP. The term "non bullous cutaneous pemphigoid"[13] has been used in the literature to describe this non-classical presentation. Up to 20% of BP patients have been reported to have this atypical subtype.[14,15] Different subtypes of this form have been described: i) eczematous; ii) urticarial; iii) pemphigoid nodularis. Plaques, papules, or nodules, with intense pruritus characterize the eczematous variant. The urticarial variant is characterized by pruritic urticarial papules and plaques.[16] Prurigo-like nodules of the distal extremities, frequently in elderly patients, characterize rarer form named "Pemphigoid nodularis". Bullae, if present, can occur before or after the onset of nodular lesions, appearing at affected or on unaffected skin.[14]

Other Rare Presentations

The vesicular BP form is characterized by multi-clustered tense vesicles with a symmetric distribution, which mimics the dermatitis herpetiformis lesions.[17] Dyshidrosiform pemphigoid is identified by pompholyx-like vesicles that develop in the palmoplantar region and then extend to other body segments.[18] Clinically, pemphigoid vegetans is described with purulent and vegetative lesions in intertriginous regions.[19] Another uncommon presentation of BP, named "Erythrodermic BP" is characterised by erythroderma with or without blistering.[20] Lichen planus pemphigoids is the clinical and histological manifestation of a lichen planus-BP overlap.[21] It typically affects young people with a relatively benign course. Although there is no clear link between BP and cancer, erythematous and more figurate lesions than classic BP forms, may be a symptom of an undiagnosed cancer.[22] Brunsting-Perry pemphigoid, mostly described in elderly males, is distinguished by the presence of recurring blisters that typically present only on the head and neck. In this case, the lesions frequently heal with atrophic scars.[23] Vulvar involvement is unusual as a localized variation of the disease,[24] which is distinguished by recurring, non-scarring vesicles and erosions limited to the vulva, well responding to topical steroids.[25] Furthermore, other rare presentations have been described in literature. Qiu et al described an interesting and rare presentation of BP in a patient treated with pembrolizumab. Particularly, in this case, the patient

presented a widespread eruption of tense bullae on an erythematous base and erosions, mimicking toxic epidermal necrolysis (TEN).[26] Another atypical presentation has been reported with palmoplantar keratoderma (PPK) in BP patients. Although dyshidrosiform pemphigoid has been shown to involve palmoplantar region, the typical histological features of these patients (lack of vesicular lesions) may categorize PPK as a novel and different presentations of BP.[27] Lichen planus pemphigoides (LPP) is a rare condition characterized by the association of blistering disease, such as BP, and lichenoid skin changes. It usually presents with tense blisters and lichenoid plaques, with typical histological features (the demonstration of autoantibody deposition along the dermal-epidermal junctional zone in perilesional skin biopsies) representing the gold standard to reach the diagnosis. LPP has been considered for long time as a variant of lichen or bullous diseases, growing evidence showed it may be considered as a separate disease entity.[28] A new clinical variant has been described in patients presenting typical clinical features of acquired reactive perforating dermatosis (ARPD) coexisting with BP, called perforating like BP. In these described cases, patients firstly presented with papules and nodules with a central keratotic plaque, developing point blisters only later. Both diabetes mellitus and haemodialysis have been suggested as causative in almost all reported cases. Interestingly, histological features were common with typical presentations of BP, showing BP180 autoantibodies were found to bind at the dermo-epidermal junction.[29] Finally, another rare clinical presentation has been described by Mahmoudi et al, which reported the atypical case of a patient presenting BP with linear lesions. Particularly, the patient reported a history of intense pruritus and generalized non-inflammatory bullous lesions, with a linear arrangement. Interestingly, no circulating anti-BP180 or anti-BP230 antibodies were found, while the patient showed only IgG antibodies directed exclusively against the 120-kDa LAD-1 antigen.[30]

Risk Factors and Linked Conditions

Aging is widely recognised as the most important risk factor for BP.[31–33] Indeed, BP is mostly a disease of elderly patients, with a reported onset around 75 years, and a clear female preponderance.[32–34] BP is less common in children, presenting clinical features comparable to adult BP, except for the more frequent and predominant involvement of acral regions. Childhood BP typically shows a better prognosis than adult forms, quickly improving when treatment is started.[35] Several neurologic illnesses have been related to an increased risk of BP. Indeed, several studies in the last ten years have highlighted the link between BP and psychiatric or neurologic diseases.[36–48] Including all, 22–46% of BP patients have been reported to present at least one neurologic disorder. Indeed, BP has been significantly associated with dementia (especially Alzheimer's disease), Parkinson's disease, epilepsy, cerebrovascular disease, and psychiatric disorders.[36,39,41–43,48] In most reported cases, BP occurred after the beginning of the neurological condition, with onset intervals ranging from a few months to more than 5 years.[40] Furthermore, BP has been linked to degenerative neurological diseases[42] including Parkinson's and Alzheimer's, which may involve immunological pathways. The delayed development of BP, in later stages of these diseases, may be probably linked to BP230 neuronal variants, recognised as non-self-structures after the rupture of immune tolerance caused by the neuronal degeneration described in some neurological degenerative disorders.[49,50] Hence, these data indicate that neurologic disorders may represent an independent risk factor for BP. Many drugs have been linked to BP.[43,51–55] Indeed, more than 50 drugs have been linked to the development of BP based on single case reports, including diuretics (eg, furosemide), antibiotics (eg, ciprofloxacin, amoxicillin), analgesics, potassium iodide, D-penicillamine, biologic therapy such as anti-tumor necrosis factor drugs and the anti-diabetic dipeptidyl peptidase-4. Although some reported drugs may represent a trigger for BP development and recurrence, more studies are needed to better clarify the exact mechanisms through which drugs may induce BP. Because both BP and cancer are diseases of the elderly, the relationship between BP and malignancy may be linked to the older age of patients. Furthermore, multiple case reports have described BP in connection with a variety of malignancies for years, with a number of these cases demonstrating a similar clinical course between internal malignancy and BP prognosis.[56] BP has been linked to several different disorders, including several psoriasis and lichen planus, with bullae frequently observed on psoriatic plaques or lichenoid papules, suggesting a Koebner phenomenon. Indeed, burns, trauma, and ultraviolet irradiation may trigger BP in some patients.[56] BP has been observed in individuals with several autoimmune diseases, including thyroiditis (both Hashimoto and Grave diseases), rheumatoid arthritis, lupus erythematosus,

dermatomyositis, autoimmune neutropenia or thrombocytopenia, and vitiligo. These associations may be linked to a hereditary predisposition to develop autoimmune disorders. However, a recent case–control study found no higher incidence of autoimmune diseases in patients with BP.[57] Because glycation of proteins at the dermal–epidermal interface may enhance their immunogenicity, a link between BP and diabetes mellitus has been hypothesized. Further case–control studies[39–43,58] did not support this association, and the high occurrence of diabetes in BP patients may be due to the higher frequency of BP in elderly patients.

Although the genetic background of BP has not been completely clarified, recent evidence suggests a genetic background. Indeed, several studies[59–66] found the HLA-DQB1*0301 in patients with BP, which may have a role in the development of BP.[62] Furthermore, recent findings showed that other gene allotypes may play a role in the genetic background of BP, including mitochondrial anomalies (MT-ATP8 gene), specific cytochrome P450 isoenzyme (CYP2D6), and an over expression of specific Fc receptor subtype (FcRIIIa) on immune cells.[66–70]

Diagnosis

The diagnosis of BP is based on typical clinical features, the finding of specific self-antibodies (indirect immunofluorescence (IF) or enzyme-linked immunosorbent assay (ELISA), and skin biopsy (direct IF microscopy)). Particularly, specific clinical characteristics and positive direct IF microscopy represent the most useful tools for BP diagnosis. In a small percentage of patients (about 10%) who have both indirect IF microscopy and ELISA negative results, additional immunopathological examinations may be required to detect the typical BP autoantibodies (anti-BP180, and anti-BP230).[71] Furthermore, most patients also show hyper-eosinophilia, and/or an elevation of total IgE levels.[72]

Clinical Criteria

BP should be suspected in older individuals who have generalized pruritus with or without prominent bullae. The first patients' evaluation should include an accurate anamnesis, looking for comorbidities and risk factors, physical examination, the assessment of BP severity, based on the use of widely recognised scores, such as the BP Disease Activity Index (BPDAI).[73–76] In most typical forms, the sparing of the head and neck, and mucous membranes hint at BP diagnosis. A comprehensive and accurate medical history is mandatory, evaluating the presence and the severity of pruritus, the date of symptoms start and their progression, any comorbidities, malignancies, and recent token medication (within the last 1–6 months). The prospective therapy of choice is influenced by associated cardiovascular illnesses and immunological deficits.[77,78] Tight, often transparent skin blisters surrounded by erythematous or urticarial plaques and moderate-to-severe itching are symptoms of BP.[4,5] A French analysis showed that the diagnosis of BP may be confirmed with high sensitivity (90% and specificity (83%), in patients with a subepidermal blistering disease and linear epidermal basement membrane deposits of IgG or C3 if these criteria are present: i) no head and neck involvement; ii) no mucosal involvement; iii) age over 70 years.[79–81] These clinical criteria, however, need an history of recent blisters, which are reported to be absent in about 20% of patients at the time of diagnosis.[33,34,82] Hence, in patients with non-bullous manifestations, such as in those presenting urticarial, erosive, or eczematous lesions, a prominent role to reach BP diagnosis is played by direct IF microscopy evaluation and the detection of typical serum antibodies (anti-BP180, and anti-BP-230).[83–85]

Immunofluorescence (IF) Microscopy

Direct IF microscopy of perilesional, nonbullies skin, represents the gold standard for autoimmune bullous disorders diagnosis. Although it is not specific, direct IF is the most sensitive diagnostic tool for BP.[86] It shows fine, linear, continuous IgG (IgG4 and IgG1) and/or complement C3 deposits along with the epidermal basement membrane (BM). IgA and IgE, even if less commonly, can also exhibit a similar pattern. A biopsy sample of early bullae can detect subepidermal blistering with inflammatory infiltration, mainly consisting of eosinophils, neutrophils, and mononuclear cells of the upper dermis, whereas the cavity of the bullae includes a net of fibrin with a heterogeneous cellular infiltrate.[4,84,85]

Direct IF microscopy examinations of perilesional skin following treatment with 0.09% NaCl solution may guide the differential diagnosis between BP and other autoimmune blistering diseases such epidermolysis bullosa acquisita,

mucous membrane pemphigoid, and anti-p200 pemphigoid. The incubation of the tissue in 1 mol/L NaCl solution induces an artificial blister at the BM, leading the skin to be tested for tissue-bound autoantibodies. BP is compatible with immune deposits seen in the BM of the blister's roof. In DIF microscopy, the "n-serrated" pattern of BP may assist distinguish it from epidermolysis bullosa acquisita, which may have an u-serrated pattern.[87]

Immune deposits can be seen on either the epidermal or both the epidermal and dermal sides of the split in BP.[88] Close examination of the linear fluorescence pattern at the BM helps distinguish BP ("n-serrated" staining pattern) from epidermolysis bullosa acquisita ("u-serrated" staining pattern).[89]

The presence of serum IgG autoantibodies binding the BM is shown by indirect IF microscopy (IIF), leading to find immune deposits on the epidermal side of the blister in BP. Salt-split skin (of healthy human skin) is the most specific IIF substrate for BP: it was demonstrated to have a 100% specificity for BP.[86,90] The salt-split normal human skin is currently the preferred substrate for IIF tests and has replaced the use of other substrates, such as the intact human skin and monkey esophagus, which showed to be not adequate for the differential diagnosis between BP and other blistering disorders. As a result, it is recommended that every patient with clinical suspect of BP undergoes IIF examination using human salt-split skin as substrate.[78] In 60–80% of patients, circulating anti-basement membrane autoantibodies of the IgG class and, less commonly, of the IgA and IgE classes are found.[11,91–96] These autoantibodies usually bind to the epidermal side of saline-separated normal human skin or, less commonly, to both the epidermal and dermal sides.[11,94,95]

Enzyme-Linked Immunosorbent Assays (ELISA)

The enzyme-linked immunoassay (ELISA) reveals the existence of circulating antibodies targeting NC16A, BP180, and BP230. Autoantibody serum levels have been observed to correlate with disease activity,[97] and high levels of anti-BP180 NC16A have been linked to an increased risk of relapsing.[98] Thus, ELISA can be employed to adjust the treatment choice.[99] Low blood levels of anti-BP180 or anti-BP230 have been found in around 4% of patients who do not have BP, particularly those with pruritic dermatoses.[100,101] Direct immunofluorescence microscopy is indicated in these cases to rule out BP.[90]

ELISAs that use recombinant proteins that include portions of the BP antigens (the C-terminus of BP230 or BP180, and NC16A domain of BP180) allow for the quick identification of autoantibodies in the blood of BP patients.[11,91,102–108] Anti-BP180 antibodies are found in 72–93% of BP patients using commercially available ELISA,[88,99–104] instead anti-BP230 autoantibodies are detected in 57–63% of BP patients.[93,96,109–112] Furthermore, while serum levels of anti-BP180 autoantibodies have been linked to disease activity,[93,109,113] anti-BP230 autoantibodies values did not correspond with disease activity,[16] although the latter did appear to be related with localized forms of BP.[103,109] In daily clinical practice, the use of ELISA for BP230 protein shows low sensitivity (5–10%), being indicated in case of a negative BP180-ELISA.[50,93,109] Immunoblot and immunoprecipitation techniques showed that 60–100% of the serum from BP patients included IgG targeting BP180 and/or BP230;[92,114–119] this serum may also include IgA and IgE autoantibodies. Nowadays ELISA has largely supplanted the technically more difficult immunoblot and immunoprecipitation procedures. These traditional, but not entirely standardized, immunochemical approaches are only used situations of BP, including ELISA BP230-negative blood samples, or BP180-negative.

Diagnosis of Bullous Pemphigoid: Practical Approach

The diagnosis of BP may be a challenge, especially in the non-bullous phase, due to non-specific manifestations which may mimic a variety of diseases, such as contact dermatitis, prurigo, drug reactions, urticaria, scabies, and acquired non-autoimmune blistering disorders (such as Stevens-Johnson syndrome, dyshidrotic eczema, bullous arthropod bites, bullous drug eruptions), which are usually differentiated by clinical history, pathologic features, and direct IF microscopy. The pemphigus disease, dermatitis herpetiformis, and paraneoplastic pemphigus are differentiated from BP with no difficulties, basing the differential diagnosis on typical clinical and direct IF findings. In elderlies presenting typical generalized blistering eruption, the diagnosis is easily made using clinical criteria and direct IF. On the other hand, atypical and localized BP forms typically does not present the clinical criteria to confirm BP diagnosis.[66,79] Hence, in these cases, the diagnosis must be confirmed by further examinations, including direct IF microscopy examination.

Furthermore, in case of BP suspect, it is mandatory to consider other autoimmune subepidermal blistering diseases with the same linear BM deposits pattern by direct IF microscopy. Particularly, patients presenting with both cutaneous and oral manifestations, the differentiation of BP from mucous membrane pemphigoid may be a challenge. Hence, to reach the right diagnosis, it is important to evaluate the limited skin involvement, the scarring mucosal tendency and the characterization of circulating autoantibodies.[120–126] Moreover, BP should be differentiated from the inflammatory form of epidermolysis bullosa acquisita, which may be excluded with IIF examination, and the characterization of serum antibodies (against type VII collagen in epidermolysis bullosa acquisita).[127–131]

In patients with non-bullous manifestations, further differential diagnosis should be considered, such as in patients presenting vesicles, urticarial lesions, and plaques. These patients have reported to be frequently younger, of Japanese origins, and frequently affected also by psoriasis.[6] These patients typically present autoantibodies that specifically bind the dermal side of salt-split human skin.[7,132] Finally, another difficult challenge among BP patients is the categorization elderly patients presenting generalized pruritus (with or without skin lesions), in which anti-BP180 and/or BP230 are found, but IF microscopy examination remains negative.[96,133–135] It is important to remark that the finding of serum antiBP-180/230 antibodies should not be considered as a diagnostic criterion for BP in the absence of typical direct IF microscopy findings.[82] However, a follow-up of these patients may be useful to detect early BP symptoms, because some of these patients, may develop BP and could be thought of as having pemphigoid incipient.

BIOCHIP Method

The BIOCHIP (Dermatology Mosaic 7, EUROIMMUN, Lubeck, Germany) method, represents a new multiplex IF technique reported in the serological diagnosis of BP.[136] Particularly, this technique combines the screening of many autoantibodies and target antigen-specific substrates in a single incubation field, leading the simultaneous processing of the most common autoimmune bullous disorders' antibodies with a single investigation.[137–139] Hence, through the presence of multiple antigens a single incubation field, this novel approach led to screen patients for most common autoimmune bullous disease autoantibody using a single investigation, providing a more efficient and cost-saving way to investigate for these conditions, and resulting particularly useful to provide a timely diagnosis in cases where a prompt treatment is required.[136] To date, the BIOCHIP has already been validated, showing high specificity and sensitivity in seven studies analysing its use in the diagnosis of BP.[136–141]

Treatment

BP is a chronic disease showing phase remissions and spontaneous exacerbations, linked with an important impact on patients' quality of life. Treatment choice is usually driven by both the severity of the disease and the general health conditions and comorbidities of patients. Indeed, due to higher comorbidity rate in BP patients, which are most frequently elderly patients, one of the most important objectives to control both itchy symptoms and skin lesions, avoiding as much as possible patients' exposure to the potential AEs linked with chosen treatment. Although a standard treatment duration is still unestablished, BP patients are frequently treated for about 6–12 months (including a maintenance phase with low-dose oral or topical steroids), except in corticosteroid-refractory cases, where a longer treatment may be required.[109] Systemic corticosteroids have been considered the first-line treatment for long time, especially in generalized forms.[71] Particularly, oral prednisone (0.5–1 mg/kg/day, progressively over a period of 6–9 months) is widely considered the most used treatment, leading to reach disease control usually within 2 weeks. The main problem, linked with the use of systemic steroids in elderly patients, is represented by the significant high rate of adverse effects, which may result in a higher mortality and increased adverse than topical clobetasol propionate 0.05%.[71] Indeed, based on the results two randomized controlled trials, potent topical steroids (clobetasol propionate 0.05% cream) should be considered as first-line treatment whenever possible, with similar clinical outcomes and lower AEs rate than systemic treatments.[75,76] Immunosuppressive drugs, such as azathioprine, methotrexate, and mycophenolate mofetil, should be considered to reduce systemic steroid dosage, and as second-line treatment in case of failure or contraindications to systemic steroids.[71,90] Among immunosuppressive drugs, azathioprine (1–3 mg/kg/day orally) is the most frequently used in the management of BP.[50] Other reported treatments that have been reported in the treatment of BP include i) the combination of nicotinamide (at the dosage of 500–2500 mg/day) and tetracyclines (200 mg/day orally); ii) topical

immunomodulators (tacrolimus ointment); iii) and few cases treated with biological drugs, including rituximab, an anti-CD20, and etanercept an anti-TNFα. However, these treatments showed contrasting results and their role in the treatment of BP is still not well clarified.[142–145]

Monitoring

Since systemic therapies may be necessary for a long time in BP patients, the severity of the disease should be thoroughly evaluated at baseline and follow-up sessions to evaluate clinical response to treatment as well as any AEs during follow-ups. Both clinical and biological monitoring should be considered. Regarding clinical monitoring, it is currently advised that disease severity and treatment response should be assessed using BP-specific criteria and outcome measures. BP Disease Area Index (BPDAI) score is the most used and accepted score to evaluate disease severity.[74] This score considers all the following aspects: body sites affected (with separate scores for skin and mucosal involvements), the type of lesions (differentiated in transient and non-transient), the number of the lesions (considering blisters, eczematous plaques, urticarial lesions), and the severity of itch (using a separate a separate subjective component).[74] BPDAI score was established by an international BP definitions committee, resulting relevant for both clinical practice and clinical trials, in order to use a unified score and better compare clinical outcomes during treatments and to improve BP follow-up for physicians.

While clinical monitoring was well established, the biological monitoring, which is frequently based on the use of serological tests (ELISA-BP180), to guide and evaluate treatments is still not established. Indeed, although the correlation between BP activity and BP180 ELISA levels has been reported, the practical and clinical significance of ELISA values during treatments is still not well been clarified. However, it has been shown that the serum concentration of anti-BP180 antibodies, evaluated with ELISA studies, correlates with BP severity.[11,33,91] Furthermore, the fluctuation of anti-BP180 levels between baseline, day 60, and day 150 may be used as treatment outcomes predictor.[146] Indeed, even a small decrease of these levels between baseline and day 60 has been associated with a higher rate of BP relapse within the first year of treatment.[147] Moreover, other indicators found to be linked of later relapse of BP have been found in positive direct IF findings and high BP180-NC16A ELISA title.[148] Indeed, a recent study found that relapses did not occur when the ELISA values decreased to 40% of initial values, although they were still not within the normal range.[149]

Conclusions

Although our knowledge of BP pathophysiology increased in recent years, mortality and morbidity rates are still high in this disease. Indeed, several large studies showed that even with early treatment, BP patients have a prognosis comparable with a diagnosis of end-stage heart disease, reporting a mortality rate of up to 40% of patients dying within 12 months from the diagnosis.[150] This may be linked to both patients' comorbidities and immunosuppressive drugs used in BP treatments.[150] An early diagnosis, and consequently correct management, monitoring, and assessment of patients suffering from BP are crucial to improving as much as possible the prognosis of these patients. As shown, many factors may trigger BP an accurate anamnesis focused on the recognition of a possible trigger factor can improve prognosis by promptly removing it. Furthermore, most BP patients are elderly, suffering from multiple comorbidities; hence, it is important to choose the best treatment option also consider other diseases and reduce as much as possible side effects which may be linked to the prescribed treatments. It results in primary relevance also the correct assessment of disease severity. Indeed, using widely approved scores, such as BPDAI, to assess disease severity at baseline and each follow-up visit, may improve the management of the disease by choosing the right treatment at the right dosage, trying to reduce patients' exposition to possible adverse events which may be linked, for example, to higher drugs' dosage. Near to the clinical monitoring, also biological monitoring is frequently required in clinical practice. Indeed, even if a standardized definition of the best serum concentration of BP-180 antibodies levels is to reach during treatments, biological monitoring may be useful during follow-ups, due to the link between an elevation of these levels and BP flare-up. Another important aspect to consider in the management of BP patients, especially in elderlies, is to carefully check the eventual burden of any comorbidities during treatments.

In conclusion, the management of BP is still considered a challenge in dermatology, due to the high mortality rates and difficulties in treating elderly patients. However, early recognition of the disease, correct treatment choice, and monitoring during follow-up of both BP and patients' comorbidities may certainly improve patients' outcomes.

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