REVIEW ARTICLE

The Diagnosis and Treatment of Autoimmune Blistering Skin Diseases

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SUMMARY

Background: Autoimmune blistering skin diseases are a heterogeneous group of disorders associated with autoantibodies that are directed against desmosomal structural proteins (in pemphigus diseases) or hemidesmosomal ones (in pemphigoid diseases and epidermolysis bullosa acquisita), or else against epidermal/ tissue transglutaminases (in dermatitis herpetiformis). Knowledge of the clinical presentation of these disorders and of the relevant diagnostic procedures is important not just for dermatologists, but also for general practitioners, ophthalmologists, ENT specialists, dentists, gynecologists, and pediatricians.

Methods: The literature on the subject was selectively reviewed. There are no existing guidelines available in Germany.

Results: The recently developed sensitive and specific assays for circulating autoantibodies in these diseases now enable a serological diagnosis in about 90% of cases. The incidence of autoimmune blistering skin diseases in Germany has doubled in the last 10 years, to a current figure of about 25 new cases per million persons per year, because of improved diagnostic techniques as well as the aging of the population. Accurate and specific diagnosis is the prerequisite for reliable prognostication and appropriate treatment. For severe and intractable cases, more effective treatments have recently become available, including immunoadsorption, high-dose intravenous immunoglobulin, the anti-CD20 antibody rituximab, and combinations of the above.

Conclusion: The diagnostic assessment of autoimmune blistering skin diseases can be expected to improve in the near future as new serological testing systems are developed that employ recombinant forms of the target antigens. The treatments currently in use still need to be validated by prospective, controlled trials.

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Autoimmune blistering skin diseases are a heterogeneous group of conditions clinically characterized by blisters and erosions on the skin and close-to-surface mucous membranes. In pemphigus diseases, the autoantibodies are directed against desmosomal proteins, and cell contact within the epidermis is lost. In subepidermal autoimmune blistering diseases, the antibodies are directed against hemidesmosomal structural proteins, and the result is cleavage between the epidermis and the dermis *(Table 1, Figure 1)*. In this article, we will describe the clinical course of these diseases, current epidemiological trends, recently developed diagnostic tests, and treatment options. As there are no current guidelines on the subject in Germany, this article is based on a review of the pertinent literature.

Clinical features

In pemphigus, since cleavage occurs within the epidermis, blisters have a relatively thin roof and are loose and fragile; thus, skin erosion, rather than blistering, tends to be the predominant finding in pemphigus vulgaris and the nearly exclusive finding in pemphigus foliaceus *(Figure 2b)*. The main difference between these two conditions, however, lies in the degree of involvement of the mucous membranes. In pemphigus vulgaris, the mucous membranes are always involved *(Figure 2a)*, while the skin may or may not be affected; in pemphigus foliaceus, the mucous membranes always remain normal (e1). Paraneoplastic pemphigus is characterized by the associated neoplasia, marked stomatitis, and polymorphic skin changes: not just blisters and erosions, but also lichen ruber-like plaques and pustules (e2–e4). IgA pemphigus, the rarest type, is typically associated with pustule formation.

In subepidermal blistering diseases, cleavage occurs between the epidermis and the dermis; thus, the blisters have a thicker roof than the blisters of pemphigus, and are usually tense *(Figures 2c and 2d)*. Bullous pemphigoid (BP) is almost always associated with severe itch and is a disease of the elderly, with a mean age of onset of 76 years (e5). Pemphigoid gestationis manifests itself during pregnancy or in the immediate postpartal period and is also associated with severe itch. Pemphigoid gestationis usually presents without blisters but rather with eczematous, urticarial, or papular skin changes. Linear IgA dermatosis is the most common autoimmune blistering disease in children. It can clinically resemble BP (anti-laminin-γ1 pemphigoid, also

TABLE 1

Tests to establish the diagnosis of autoimmune blistering skin diseases through the use of recombinant or cellular target antigens

Disease	Commercially available ELISA	Western blot. commercially unavailable ELISA
Pemphigus		
Pemphigus vulgaris	**Desmoglein 3** **Desmoglein 1**	–
Pemphigus foliaceus	**Desmoglein 1**	–
Paraneoplastic pemphigus	**Envoplakin** Desmoglein 1 and 3, B230	**Periplakin**, desmoplakin I and II, α2-macroglobulin-like1, plectin
Subepidermal autoimmune blistering skin diseases		
Bullous pemphigoid	**BP180 NC16A**, BP230	–
Pemphigoid gestationis	**BP180 NC16A**, BP230	–
Linear IgA dermatosis	–	**Soluble ectodomain of BP180 (LAD-1)**
Mucous membrane pemphigoid	**BP180 NC16A**, BP230	**C-terminus of BP180, laminin 332**, α6β4-integrin
Lichen planus pemphigoides	**BP180 NC16A**, BP230	–
Anti-Laminin γ1 / p200 Pemphigoid	–	**Laminin γ1**
Epidermolysis bullosa acquisita	–	**Type VII collagen**
Dermatitis herpetiformis	**Epidermal/tissue transglutaminase**	–

The main target antigens are indicated in boldface type.

known as anti-p200 pemphigoid, can do this as well); in linear IgA dermatosis, however, the tense blisters are frequently seen in a ring-like arrangement. Mucous membrane pemphigoid is characterized by the predominant involvement of the mucous membranes that are near the surface of the body. Ocular involvement carries the risk of blindness. Epidermolysis bullosa acquisita has two clinical variants: an inflammatory variant resembling BP or mucous membrane pemphigoid, and a mechano-bullous variant associated with blisters and erosions at mechanically exposed sites which usually heal with scars or milia. Patients with dermatitis herpetiformis develop markedly pruritic, often excoriated papules, mainly on the extensor surfaces of the limbs, on the scalp, and on the buttocks. Blisters, on the other hand, are rare.

Incidence

In Germany, there are an estimated 2000 new cases of autoimmune blistering skin diseases per year, with an overall prevalence of about 12 000 cases. The incidence of pemphigus in Central Europe is one to two cases per million persons per year, and 80% of pemphigus patients have pemphigus vulgaris (e6). BP is the most common type of subepidermal autoimmune blistering skin disease in Central Europe, with an incidence of about 13 cases per million persons per year; the next most common types are mucous membrane pemphigoid and pemphigoid gestationis (1, e7–e10). The incidence of BP in Great Britain was recently reported to be twice as high as this, though there is reason to suspect that this estimate is too high as a result of the particular epidemiological methods by which it was derived (1). Interestingly, the incidence of BP in Germany has nearly doubled in the last ten years (e7, e8). This is probably due to improved diagnosis as well as to the aging of the population. BP is the only autoimmune disease whose incidence increases with advancing age: among persons over age 80, its incidence is between 150 and 180 per million persons per year (e9, e11). BP is often preceded by a non-blistering premonitory stage with marked itch and should thus always be excluded in an elderly patient presenting with pruritus; currently, this can usually be done serologically.

Diagnostic evaluation

Direct immunofluorescence

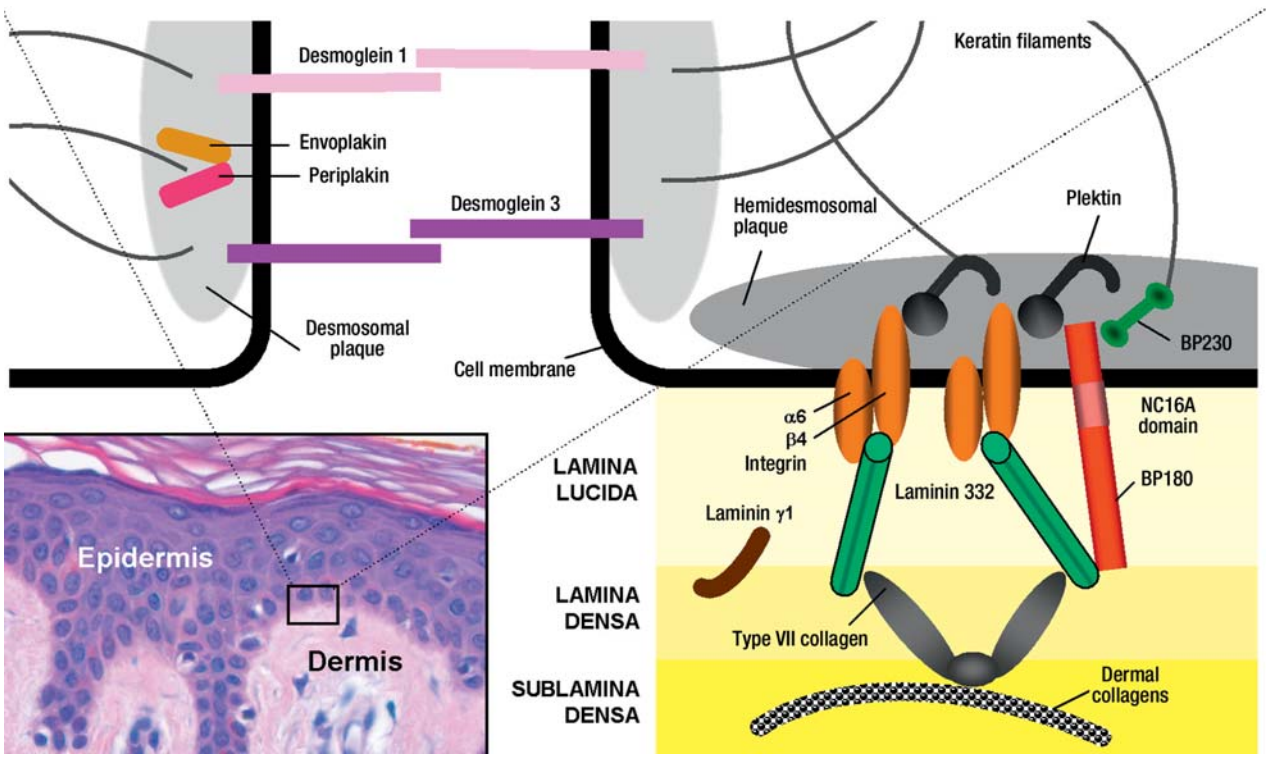
The current gold standard of diagnostic testing for autoimmune blistering skin diseases is direct immunofluorescence (IF) microscopy to demonstrate tissue-bound autoantibodies and/or of C3 in the patient's skin or mucous membranes (e12). By direct IF microscopy pemphigus and subepidermal blistering diseases can be differentiated.

Serological tests

Indirect IF microscopy of the patient's serum can be used as a screening test for circulating antibodies. Indirect IF microscopy on monkey or guinea pig esophagus has become an established mode of testing for serum antibody in pemphigus *(Figure 3a)*; for the subepidermal autoimmune blistering diseases, the preferred substrate is normal human skin that has been split with 1 M sodium chloride solution *(Figures 3b and 3c)* (e13). In patients with dermatitis herpetiformis, IgA reactivity against the endomysium can be visualized on monkey esophagus (e14). Definitive diagnostic testing follows, with the aid of various ELISA or Western blot studies involving the relevant target antigens *(Table 1)*. Some of these ELISAs are commercially available *(Table 1)*. Nowadays, these tests usually suffice to establish the diagnosis by serology in conjunction with a compatible clinical picture.

For the diagnosis of pemphigus vulgaris and pemphigus foliaceus, sensitive and specific commercial ELISAs for the detection of antibodies against desmoglein 1 and 3 are available (2, e15, e16). The great majority of patients with paraneoplastic pemphigus show reactivity to envoplakin and/or periplakin (e17–e19), which can be detected by immunoblotting with extract of cultured human keratinocytes, or else in a recently developed ELISA employing a recombinant envoplakin N-terminal fragment (e19). In BP, the 16th non-collagenous domain (NC16A) is the immunodominant region of BP180; IgG autoantibodies against it are

FIGURE 1



A schematic view of desmosomal and hemidesmosomal target antigens in autoimmune blistering diseases, and the interactions between them. In the histological section of normal skin at bottom left, one sees the epidermis, the dermis, and the dermo-epidermal junctional, also called the basal membrane, zone, which connects the epidermis to the dermis. Two neighboring basal keratinocytes are shown schematically. Pemphigus diseases are histologically characterized by intraepidermal cleft formation; their target antigens are desmosomal structural proteins by means of which neighboring keratinocytes adhere to each other. The desmosomal target antigens of the pemphigus diseases include desmosomal plaque proteins (envoplakin, desmoplakin, periplakin) and transmembrane proteins of the cadherin group (desmoglein 1 and 3, desmocollin 1) whose extracellular portions mediate the adhesion of neighboring keratinocytes (left side of diagram). Hemidesmosomal proteins anchor the epidermis to the dermis and are the target antigens in subepidermal autoimmune blistering skin diseases, in which cleavage occurs between the dermis and the epidermis (right side of the diagram). Hemidesmosomal plaque proteins (BP230, plectin) interact with the transmembrane proteins BP180 and α6β4-integrin, which, in turn, are connected by way of laminin 332 to type VII collagen. Type VII collagen establishes a connection to dermal collagens. Proteins that have not been found to be targets of autoantibodies are not included in this diagram.

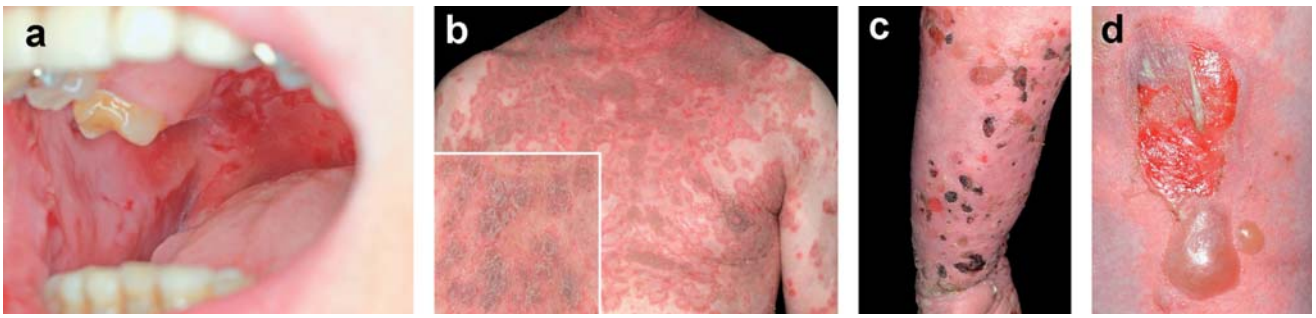


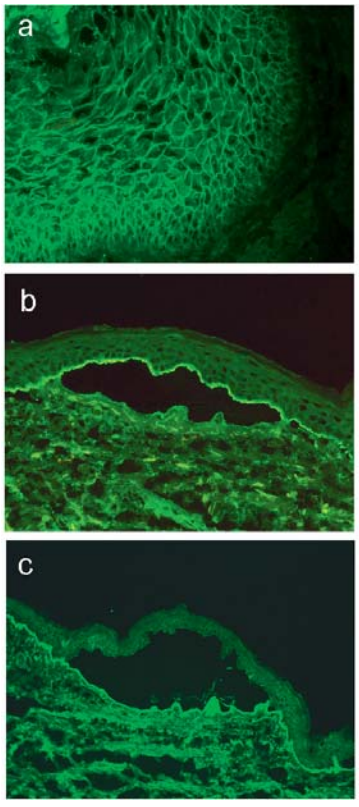
Figure 2: The clinical features of autoimmune blistering skin diseases.

a) Multiple buccal erosions in a woman with pemphigus vulgaris. Only the oral cavity is involved; the serum autoantibodies react exclusively with desmoglein 3.

b) Widespread erythematous plaques, urticarial erythema, and erosions with superficial scaling on the chest of a man with pemphigus foliaceus. The autoantibodies are directed exclusively against desmoglein 1.

c,d) Tense blisters filled with serous fluid, erosions, and crusts on both erythematous and normal-appearing skin, on the arm of a woman with bullous pemphigoid.

FIGURE 3



Indirect immunofluorescence. Indirect immunofluorescence microscopy is used as a screening test for serum autoantibodies in autoimmune blistering skin diseases. The most sensitive substrates currently used include monkey esophagus for pemphigus vulgaris and pemphigus foliaceus (a) and human skin split with 1 M NaCl solution for pemphigoid diseases (b, c). Antibodies against type XVII collagen (BP180) and BP230 bind to the epidermal side of the artificial cleft (b), while antibodies against laminin 332 (previously known as laminin 5 or epiligrin), antibodies against the laminin γ1 chain (p200 antigen), and antibodies against type VII collagen bind to its dermal side (c). The target antigens and the corresponding diseases are shown on the right side.

present in about 85% of patients with BP (e20, e21). Interestingly, most BP patients also develop IgA and IgE antibodies against BP180 (e22–e25). 60% to 70% of BP patients have circulating autoantibodies against BP230 (e26–e28), but the presence of these antibodies is much less specific than that of anti-BP-180 antibodies for the diagnosis of BP and is not correlated with disease activity *(Table 1)* (e26). A common observation in autoimmune blistering skin diseases is that a single patient can have autoantibodies recognizing multiple epitopes on a single target antigen, or on multiple target antigens; this is called intra- or intermolecular epitope spreading (e29).

In pemphigoid gestationis, immune reactivity is essentially limited to the NC16A domain of BP180 (e30–e33); on the other hand, in linear IgA dermatosis, the autoantibodies (which are characteristically of the IgA isotype) typically react with the soluble ectodomain of BP180 *(Table 1)* (e34, e35).

In mucous membrane pemphigoid, autoantibodies can be detected in only half of all patients with indirect IF microscopy on human split skin. These autoantibodies are mostly directed against BP180 (e36–e38); in about one-quarter of patients, antibodies against laminin 332 are found (e36, e39). The detection of the latter has a special significance, as 25% of patients who have them harbor a malignant neoplasm *(Table 1)* (3, e40).

The target antigen of the disease that was initially called anti-p200 pemphigoid (4) has recently been identified as the laminin-γ1 chain (5). Patients with epidermolysis bullosa acquisita develop antibodies against type VII collagen (6), with the NC1 domain as the immune-dominant region (e41). Dermatitis herpetiformis is the cutaneous manifestation of celiac disease (sprue). In celiac disease, there are typically autoantibodies against endomysium and tissue transglutaminase; additional autoantibodies against epidermal transglutaminase are responsible for the cutaneous signs of the disease *(Table 1)* (7, e42).

Serological tests over the course of the disease

Autoantibodies against desmoglein 1 (in pemphigus foliaceus), desmoglein 3 (in pemphigus vulgaris), and the NC16A domain of BP180 (in BP) are correlated with disease activity (2, 8, e43). The corresponding ELISAs are, therefore, suitable tests for monitoring disease activity over time and can be a useful aid in setting the optimal dose of the immunosuppressive medication(s) used to treat the disease.

First-line treatments

The treatment of autoimmune blistering skin diseases is problematic, because few prospective therapeutic trials have been performed in this field to date. The trials concerning BP and pemphigus have been summarized in Cochrane reviews (9, 10). The authors of the review on BP conclude that the application of topical steroids over a wide area is well-documented as a safe and effective treatment for this disease, and they state that the initial prednisolone dose should not exceed 0.75 mg/kg/d (9). For pemphigus vulgaris and pemphigus foliaceus, there have been too few therapeutic trials to enable any recommendation about treatment (10). No guidelines for the treatment of autoimmune blistering skin diseases have been issued to date in Germany; thus, our discussion here will be based on the guidelines of the British Association of Dermatologists (11, 12), as well as on an international consensus conference on the treatment of mucous membrane pemphigoid (13), a recent survey of 32 German dermatology departments (e44), and selected reviews (e45–e48).

Monotherapy of pemphigus with oral corticosteroids causes frequent side effects, including systemic infections (70%, of which 25% are lethal), diabetes mellitus (45%), osteoporosis (30%), thromboses (15%), and gastrointestinal ulcers (15%) (e49). Thus, in the treatment of pemphigus, systemic corticosteroids are given

almost exclusively in combination with other immunosuppressive drugs such as azathioprine, mycophenolate mofetil, mycophenolate sodium, cyclophosphamide, and methotrexate *(Table 2)* (10, 11, e50, e51). Beissert et al., in a prospective, controlled study, found no significant difference between azathioprine (2 mg/kg/d) and mycophenolate mofetil (2 g/d) with respect to either efficacy or side effects when both drugs were given in combination with oral methylprednisolone (2 mg/kg/d) (15). In contrast, Chams-Davatchi et al. found a corticosteroid-sparing effect of azathioprine (2.5 mg/kg/d) compared to mycophenolate mofetil (2 g/d) both given in combination with oral prednisolone (2 mg/kg/d) (16). Recently, El Darouti et al. carried out a therapeutic trial on 64 patients with pemphigus vulgaris and reported a significantly better clinical effect from adjuvant pentoxyphylline in combination with sulfasalazine than from high-dose corticosteroids with cyclophosphamide (e53). The combination of pentoxyphylline and sulfasalazine exerts its effects by blocking TNF-α (e53). A recent controlled prospective trial involving 94 patients with pemphigus vulgaris who took prednisolone (1–2 mg/kg/d) combined with either mycophenolate mofetil (2–3 g/d) or placebo did not reveal any significant difference with respect to the primary endpoint (the percentage of patients who had no lesions and took no more than 10 mg of prednisolone daily after one year of treatment). This trial did reveal a higher rate of adverse effects in the mycophenol atmofetil group, yet the rate of *serious* adverse events was lower in this group, while the response rate was higher, and the patients remained free of lesions or recurrences for a longer time (e54).

Subepidermal autoimmune blistering diseases can be treated with the immunosuppressant drugs that are used to treat pemphigus (see above), or else with dapsone or tetracycline; all of these agents are given in combination with topical or systemic corticosteroids *(Table 2)* (9, 12). The effects of dapsone and tetracycline in BP are now being studied in controlled prospective trials. Dapsone suppresses the local cutaneous immune response by inhibiting neutrophil function and chemotaxis. It is the drug of first choice in linear IgA dermatosis, dermatitis herpetiformis, and uncomplicated mucous membrane pemphigoid without ocular involvement (e55, e56). Moreover, high-potency topical corticosteroids have been shown to be just as effective as oral prednisolone (0.5 mg/kg/d) in the treatment of BP, but with significantly fewer side effects (29% versus 54%) (14, e52). In mucous membrane pemphigoid with ocular involvement, adjuvant cyclophosphamide seems to be the most effective treatment (e57–e59).

TABLE 2

First-line treatments for autoimmune blistering skin diseases[*1]

Disease	Treatment
Pemphigus	
Pemphigus vulgaris Pemphigus foliaceus	Prednisolone (1.0–2.0 mg/kg/d[*2])[*3] + azathioprine or mycophenolate mofetil or cyclophosphamide
Paraneoplastic pemphigus	Treatment of malignancy + prednisolone (0.5–1.0 mg/kg/d[2]) + cyclosporine or cyclophosphamide or rituximab
IgA pemphigus	Dapsone or acitretin + prednisolone (0.5–1.0 mg/kg/d[2])
Subepidermal autoimmune blistering skin diseases	
Bullous pemphigoid	Clobetasone propionate 0.05% cream (10–30 g/d)[*4] + dapsone or doxycycline or azathioprine or methotrexate
Pemphigoid gestationis	Topical class II or III corticosteroids + prednisolone (0.25 mg/kg/d[*2]) + clemastine[5]
Linear IgA dermatosis	Prednisolone (0.25–0.5 mg/kg/d[*2])[*4] + dapsone
Mucous membrane pemphigoid	
– without ocular involvement	Prednisolone (1.0 mg/kg/d[*2])[*3] + dapsone or azathioprine or mycophenolate mofetil
– with ocular involvement	Prednisolone (1.5–2.0 mg/kg/d[*2])[*3] + cyclophosphamide
Lichen planus pemphigoides	Prednisolone (0.5 mg/kg/d[*2]) + acitretin + psoralen-UVA
Anti-laminin γ1/p200 pemphigoid	Prednisolone (0.25–0.5 mg/kg/d[*2])[*4] + dapsone
Epidermolysis bullosa acquisita	Prednisolone (1.0–2.0 mg/kg/d[*2])[*3] + azathioprine or mycophenolate mofetil + colchicine
Dermatitis herpetiformis	Gluten-free diet + dapsone

[*1] In the absence of German treatment guidelines, this list is based on the guidelines of the British Association of Dermatologists (11, 12), an international consensus conference on the treatment of mucous membrane pemphigoid (13), a survey of German dermatological clinics (e44), and selected review articles, including two Cochrane reviews (9, 10, e45–e47).

[*2] Initial dosage; the dose can be lowered depending on the clinical response.

[*3] Alternatively, i.v. dexamethasone pulses (100 mg on each of three consecutive days) every three weeks, and at longer intervals thereafter.

[*4] It was shown in two controlled, prospective studies that clobetasone propionate 0.05% cream (10–30 g/d) in a tapering dose is just as effective as prednisolone (0.5 mg/kg/d), but with fewer side effects (14, e52).

[*5] Not approved for use by pregnant women

Treatment options for severe and intractable cases

While BP, linear IgA dermatosis, pemphigoid gestationis, anti-laminin-γ1 pemphigoid, and dermatitis herpetiformis usually respond well to treatment *(Table 2)*, the treatment of pemphigus, mucous membrane pemphigoid, and epidermolysis bullosa acquisita is often more difficult. Further therapeutic options for such cases include high-dose intravenous immunoglobulins, immunoadsorption, and rituximab.

Intravenous immunoglobulins (IVIG)

There have been reports of the use of IVIG in more than 200 patients with autoimmune blistering skin diseases, mainly pemphigus and mucous membrane pemphigoid, nearly all of whom showed clinical improvement (17, e60, e61). Recently, the efficacy of IVIG in pemphigus was unequivocally demonstrated in a prospective, multicenter, placebo-controlled trial

(17). The most common dose of IVIG is 2 g per kilogram of body weight daily for five consecutive days; for patients with normal renal function, the entire dose can also be given over two days (e62, e63). The therapeutic benefit is enhanced by the simultaneous administration of immunosuppressive drugs (e61, e62, e64). IVIG is given every four weeks until all of the lesions are healed, and at lengthening intervals thereafter (e62). IVIG has fewer side effects than other adjuvant treatments: the infusion causes headache, fever, and shaking chills in about 25% of patients, and myalgia, arterial hypotension, tachycardia, and gastrointestinal symptoms in less than 5% (e65). The German Dermatological Society recently issued guidelines on the indications, treatment protocol, duration of treatment, and evaluation of the therapeutic benefit of IVIG in the treatment of autoimmune blistering skin diseases (18).

Immunoadsorption

In immunoadsorption (IA), immunoglobulins are selectively removed from the blood. Autoantibodies have been shown to play a major role in the pathogenesis of pemphigus, BP, and epidermolysis bullosa acquisita (8, 19, 20, e66–e68); thus, antibody removal is a rational treatment for these diseases. Unlike plasmapheresis, IA is not based on the substitution of fresh-frozen plasma or human albumin. IA can be performed either with disposable absorbers or with reusable systems. The latter are much more effective than the former, enabling a 75% reduction of autoantibodies in a single IA and a 95% reduction when IA is performed on three consecutive days (21, e69–e71).

Various protocols for the use of IA to treat autoimmune blistering skin diseases have been tested, always in combination with immunosuppressants (21, e69–e71). In all of these studies, the induction phase consisted of three or four IA treatments on consecutive days, usually with high-affinity adsorbers. All patients benefited from the treatment, 20% of the patients with pemphigus had a complete remission (healing of all lesions and discontinuation of immunosuppressive drugs), and 50% of them had a clinical remission (healing of all lesions, while immunosuppressive drugs were still given). The main advantage of IA is its rapid clinical effect: it often results in the healing of all lesions within a few weeks (21, e69, e72). An expert panel recently issued detailed recommendations on the use of IA to treat autoimmune blistering diseases (22).

Rituximab

Treatment with rituximab removes CD20-positive B-lymphocytes from the circulation for three to nine months, and has been found to be effective against autoimmune blistering skin diseases—mainly pemphigus, which was the diagnosis in over 90% of the reported cases. In roughly 80% of the patients with pemphigus, all lesions were healed over the intermediate or long term (23, e73). Rituximab was almost always given as an adjuvant drug, i.e., in addition to another type of immunosuppressive treatment. The reported complications of rituximab treatment in patients with autoimmune blistering skin diseases include infections, deep venous thrombosis of the lower limbs, pulmonary embolism, long-term hypogammaglobulinemia, and neutropenia, with an overall mortality of 4% (24, e73, e74). Rituximab can be given together with IA in order to combine the rapid improvement that is achievable with IA (21) with the excellent long-term results of rituximab; this has been done successfully in a few centers (25, e75). A consensus conference has established the indications, contraindications and dosage of rituximab treatment for autoimmune blistering skin diseases, as well as the variables that should be monitored over the course of treatment, and the criteria for discontinuing rituximab (25).

KEY MESSAGES

- Autoimmune blistering skin diseases comprise about a dozen entities. They can be divided into pemphigus diseases and subepidermal bullous diseases. In pemphigus, the autoantibodies are directed against intercellular contact structures (desmosomes); in the pemphigoid diseases, they are directed against adhesion molecules of the basal membrane zone (hemidesmosomes).
- The incidence of autoimmune blistering skin diseases in Germany has doubled over the past 10 years to its current value of 25 new cases per million persons per year. Bullous pemphigoid is by far the most common of these diseases.
- The diagnostic gold standard is direct immunofluorescence microscopy of a perilesional biopsy. Today, however, the diagnosis can nearly always be made by serological testing in conjunction with a compatible clinical picture.
- Precise diagnosis is a prerequisite for accurate prognosis and effective treatment.
- No treatment guidelines are available in Germany to date. Expert recommendations have been issued on the use of immunoadsorption, rituximab, and IVIG for patients whose disease is severe or difficult to treat.

Perspectives

More people will need treatment for autoimmune blistering skin diseases in the future as the population ages and improved diagnostic testing makes diagnosis more likely. New standardized tests for all of these diseases are being developed. Specific and well-tolerated treatments are urgently needed; rituximab, infliximab, etanercept, leflunomide, doxycycline, omalizumab, and immunoadsorption are now being tested in controlled prospective trials (see www.clinicaltrial.gov).

Conflict of interest statement
The authors state that they have received honoraria and payments of travel expenses from Roche AG and from Fresenius Medical Care. They also have a scientific cooperation with Eurimmun AG.

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REVIEW ARTICLE

The Diagnosis and Treatment of Autoimmune Blistering Skin Diseases

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