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INVITED ARTICLE

Epidermolysis bullosa acquisita: What's new?

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ABSTRACT

Type VII collagen is an adhesion molecule of the extracellular matrix in epithelial basement membranes, and the main constituent of anchoring fibrils at the dermal–epidermal junction (DEJ). Autoimmunity against this protein is causing the rare organ-specific epidermolysis bullosa acquisita (EBA). EBA is a rare acquired, heterogeneous, chronic blistering disease of skin disease of skin and mucous membranes characterized by subepidermal blisters and tissue-bound as well as circulating autoantibodies to the DEJ. EBA has several distinct clinical presentations with other subepidermal bullous diseases, such as mainly dystrophic epidermolysis bullosa or bullous pemphigoid. The circulating immunoglobulin G autoantibodies for EBA react with a 290-kDa dermal protein, type VII collagen, as detected by immunoblot analysis using dermal extracts. The pathogenicity of these autoantibodies has been demonstrated by experimental animal models, in which anti-type VII collagen antibodies injected into a mouse produced an EBA-like blistering disease in the animal. EBA cases often require high doses of systemic corticosteroids and a variety of immunosuppressants. Although treatment for EBA is frequently difficult and unsatisfactory, some therapeutic success has been reported with colchicine, dapsone, infliximab and i.v. immunoglobulin. In this review, we will focus on recent progress in our understanding of the clinical manifestations, the etiopathogenesis as well as the management of EBA.

Key words: clinical manifestations, epidermolysis bullosa acquisita, pathogenesis, therapy.

INTRODUCTION

Autoimmune blistering skin diseases are a group of severe, potentially long and life-threatening diseases, clinically characterized by blisters and erosions of skin and/or mucous membranes. Autoimmune blistering skin diseases develop autoantibodies reactive with the epidermal keratinocyte cell surfaces or the epidermal basement membrane zone, which in turn induce separation between epidermal keratinocytes or at the dermal–epidermal junction.[1,2] Based on histopathological, immunological and clinical criteria, autoimmune bullous diseases are classified into two major groups associated with autoantibodies to desmosomal (pemphigus group) or hemidesmosomal proteins (subepidermal blistering diseases, e.g. pemphigoid diseases and epidermolysis bullosa acquisita [EBA]).[3–5]

The term ''epidermolysis bullosa acquisita'' was proposed as a descriptive clinical diagnosis for patients with adult onset and features resemble those of hereditary dystrophic epidermolysis bullosa were reported by Elliott in 1904.[6] In 1971, Roenigk *et al.*[7] was the first to distinguish, on the basis of distinctive clinical and histological features, EBA from other bullous diseases, suggesting the first diagnostic criteria

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for EBA. After that, during the 1970s and 1980s, characteristic clinical, histological, immunohistological and serological features of EBA were categorized.[8–10]

Epidermolysis bullosa acquisita is a chronic blistering disease of skin and mucous membranes characterized by subepidermal blisters and tissue-bound as well as circulating autoantibodies to the dermal–epidermal junction.[11–13] The circulating immunoglobulin (Ig)G antibodies in EBA react with a 290-kDa dermal protein, type VII collagen, which is the main constituent of anchoring fibrils located at the dermal–epidermal junction, an adhesion molecule of the extracellular matrix in epithelial basement membranes. EBA is a rare disease with a prevalence of approximately 0.2/million people.[14,15] There is no sex and racial predilection known, although several studies have reported an increased occurrence of the human leukocyte antigen (HLA)-DR2 allele in patients with EBA and bullous systemic lupus erythematosus (SLE).[16,17] This HLA phenotype has been associated with hyper-immunity which suggests an autoimmune etiology for EBA. The significance of certain HLA-DR2 molecules in the pathogenesis of EBA needs to be demonstrated in the context of specific autoantigens in future laboratory investigations.[16,17]

Although EBA represents the rare autoimmune blistering disease in general, therapy for patients with EBA remains unsatisfactory, and mainly relies on immunosuppressive agents such as methotrexate, azathioprine or cyclophosphamide.[18–21] Thus, there is a need for the identification of safe and effective alternatives for treatment of EBA. In this review, we will focus on recent progress in our understanding of the pathogenesis of EBA, the characterization of clinical manifestations, and their role in maintenance.

THE AUTOANTIGENS OF EBA

Type VII collagen, the main constituent of anchoring fibrils, was identified as the autoantigen of EBA.[22,23] Anchoring fibrils are thought to anchor the epidermis and its underlying basement membrane zone to the papillary dermis.[24] Type VII collagen is composed of three identical α-chains, each consisting of a 145-kDa central collagenous triple helical portion, flanked by a large 145-kDa amino terminal non-collagenous domain (NC1), and a smaller 34-kDa carboxy-terminal non-collagenous domain (NC2). In the extracellular space, type VII collagen molecules form anti-parallel tail-to-tail dimers stabilized by disulfide bonding through a small carboxy-terminal overlap (NC2), while a fragment of the NC2 domain is proteolytically removed.[25] Several dimers aggregate laterally to form the unique cross-banded structure, namely, anchoring fibrils, which comprise anti-parallel dimers and contain NC1 domains at both ends, locating in the lamina densa and forming semicircular loops visible by electron microscope.[26] Previous studies have established that the major antigenic epitopes of type VII collagen are located within the NC1 domain of type VII collagen.[27–30]

The autoimmune nature of EBA and the pathogenic relevance of antibodies against type VII collagen are supported by the following compelling evidence. Patients' autoantibodies to type VII collagen were shown to recruit and activate leukocytes *ex vivo* resulting in dermal–epidermal separation in cryosections of human skin.[31,32] Recently, two different animal models of EBA were established: The disease can be induced in mice by injection of autoantibodies against type VII collagen into mice, when passively transferred into mice.[33,34] In this ''passive'' EBA model, skin lesions develop in all strains of mice investigated so far.[33] Subepidermal blisters can also be induced in mice by immunization with a recombinant fragment of the murine NC1 domain (GST-mCOL7C). Disease development in this ''active'' model is restricted to certain strains of mice; for example, SJL.[35,36] Both models duplicate the clinical, histological and immunological features seen in patients with EBA. Furthermore, complement activation and infiltration of granulocytes into the skin are required for blister formation in experimental EBA.[37,38] Although mechanisms of tissue damage and blister formation in EBA are not fully understood, mechanisms by which EBA autoantibodies are thought to be initiated by the binding of the autoantibodies to antigenic sites, most commonly located within the NC1 domain of type VII collagen.[27–30] Subsequently, complement is activated by the Fc-portion of autoantibodies,[37] leading to the recruitment of neutrophils,[38] which release reactive oxygen species,[32,38] ultimately resulting in subepidermal blister formation. EBA patients have a decrease in normally functioning anchoring fibrils secondary to an abnormality in their

immune system in which they produce ''pathogenic'' autoantibodies against type VII collagen.[13]

CLINICAL PRESENTATION

Cutaneous manifestations in EBA are heterogeneous and may mimic other bullous diseases. Although the clinical spectrum of EBA is still being defined, EBA patients have two major clinical subtypes: an inflammatory and a non-inflammatory phenotype (Fig. 1).[9,10] The mechanobullous, non-inflammatory form of EBA, so-called classic EBA, comprising the majority of cases, is characterized by the appearance of skin fragility and tense blisters, vesicles or bullae, with some being hemorrhagic or erosions localized to the extensor skin surface. The lesions heal with scarring and milia formation.[7] In general, lesions may appear on any mucocutaneous surface and located primarily on anatomic areas subjected to repetitive minor trauma, such as the extensor upper extremities, for example, elbows, knees, buttocks, dorsal feet, dorsal hands and toes. A group of patients with predominant mucosal disease who have autoantibodies to type VII collagen have been reclassified as mucous membrane pemphigoid patients in a recent consensus meeting.[39] Post-inflammatory hyper- and hypopigmentation are also commonly observed as well as nail dystrophy. EBA patients with the mechanobullous classic form may resemble hereditary dystrophic epidermolysis bullosa clinically, such as scarring, loss of hair on the scalp, loss of nails, and esophageal stenosis or esophageal involvement.

In addition to the mechanobullous classic variant, several inflammatory subtypes of EBA were described, clinically mimicking bullous pemphigoid, linear IgA disease, mucous membrane pemphigoid or Brunsting–Perry pemphigoid.[40–48]

Although the original diagnostic criteria for EBA stated that disease onset should be in adulthood, several childhood cases have been documented. Interestingly, several previous reports described that some childhood EBA patients with reactivity to the triple-helical collagenous domain, as well as the NC1 and NC2 domains, were of the inflammatory type.[49–52] To date, although the relationship between the epitope profile and the clinical features (particularly classical non-inflammatory vs inflammatory EBA) remains to be elucidated at the present, suggesting that reactivity with a different epitope, such as the NC1 domain and other domains, leads to the different clinical phenotypes. One possible mechanism is that, when the patient's serum react with the region other than NC1 domain, a clinical phenotype of inflammatory type presents, further suggesting the possible causative role of such autoantibodies on complement activation and inflammatory infiltrates, which in turn develops the inflammatory type of EBA. Further studies on a large number of patients with EBA should characterize the epitope specificity of EBA autoantibodies and their correlation with clinical features, such as age at disease onset, extent of skin lesions and clinical course.

Autoantibodies against type VII collagen are also responsible for bullous SLE.[53–55] EBA associated with systemic diseases have been also often reported, including rheumatoid arthritis and diabetes mellitus, as well as cryoglobulinemia and psoriasis.[56–60] An association between EBA and inflammatory bowel disease (IBD) has been extensively documented; in particular, Crohn's disease has been described in approximately 30% of EBA patients.[61–65] However, to date, their relevance for the pathogenesis of both IBD and EBA is still unclear.

HISTOPATHOLOGICAL AND IMMUNOPATHOLOGICAL FEATURES

The histological picture of lesional EBA skin typically shows subepidermal blister accompanied by various degrees of dermal inflammatory infiltrate.[66] In detail, classic EBA usually presents with a non- or pauci-inflammatory subepidermal blister, whereas the inflammatory forms of EBA are associated with a neutrophil-rich infiltrate with variable numbers of eosinophils and mononuclear cells (Fig 2a).[67] As an ultrastructural observation, in general, it has been reported that blister formation in conditions occurs beneath the region of the lamina densa by electron microscope (Fig. 3a).[22,68] These studies have been carried out using skin from patients with active EBA, obtained by biopsy. In some EBA patients, the split localizes to the lamina lucida of the dermal–epidermal junction.[69] Direct immunoelectron microscopic studies reveal immunoreactants within the lamina densa, and/or sub-lamina densa of the basement membrane

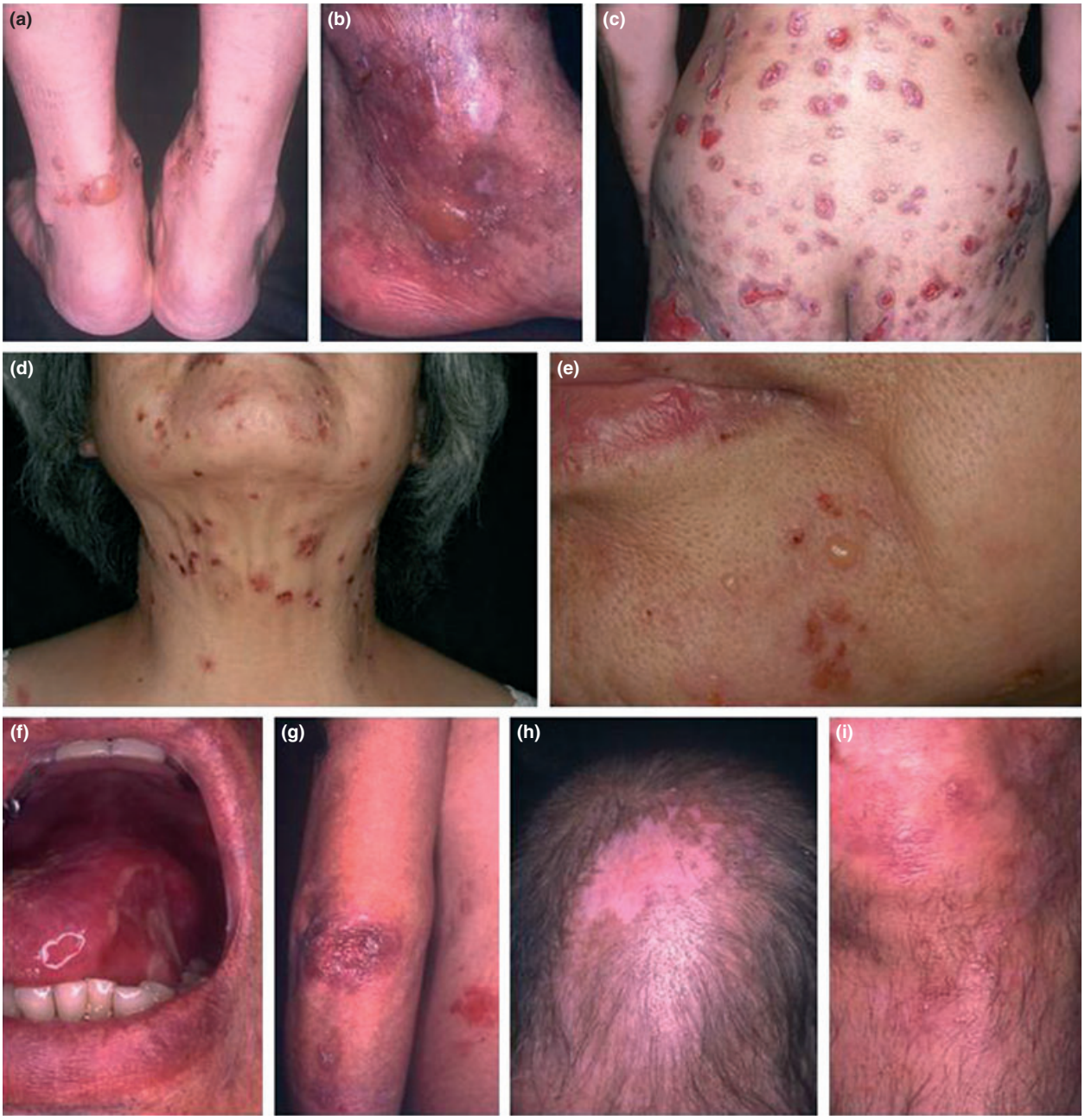

Figure 1. Clinical appearance of epidermolysis bullosa acquisita (EBA). Skin fragility and tense blisters on the heel and ankles, located primarily on anatomic areas subjected to repetitive minor trauma (a,b). Erosive lesions on the back and buttock (c). Blisters and erosions with erythematous atrophic plaques on the neck (d) and face (e). EBA also present with mucosal involvements (f). The lesions heal with scar (g), scarring alopecia (h) and milia formation (i), following blister.

zone.[70] Post-embedding indirect immunoelectron microscopic study revealed that most EBA sera showed a broad immunoreactivity within the lamina densa, whereas some sera located in the dermis below the lamina densa (Fig. 3b).[71–73]

IMMUNOFLUORESCENCE STUDIES

Direct immunofluorescence microscopy of perilesional skin biopsies from patients with EBA demonstrates linear deposits of IgG and/or C3 at the

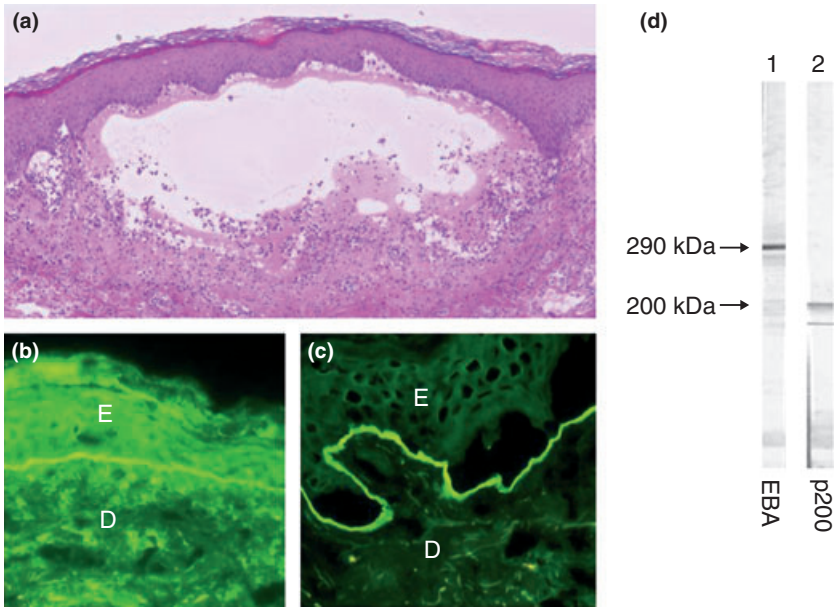

Figure 2. Histopathological and immunopathological features of epidermolysis bullosa acquisita (EBA). Histopathological findings of a perilesional skin biopsy reveals a subepidermal blister with numerous neutrophils in the upper dermis and blister cavity (a). Indirect immunofluorescence microscopy using serum from a patient with EBA shows linear deposits of immunoglobulin (Ig)G along the basement membrane zone (b). Indirect immunofluorescence microscopy on NaCl-split normal human skin demonstrates circulating IgG autoantibodies binding to the dermal side of the split (c). Immunoblot reactivity patterns of sera from patients with EBA and anti-p200 pemphigoid. Lane 1, serum of a patient with epidermolysis bullosa acquisita (EBA) reacts with 290-kDa full-length type VII collagen. Lane 2, serum of a patient with anti-p200 pemphigoid recognizes a 200-kDa protein in dermal extract. Migration of molecular weight markers is shown on the left. E, epidermis; D, dermis.

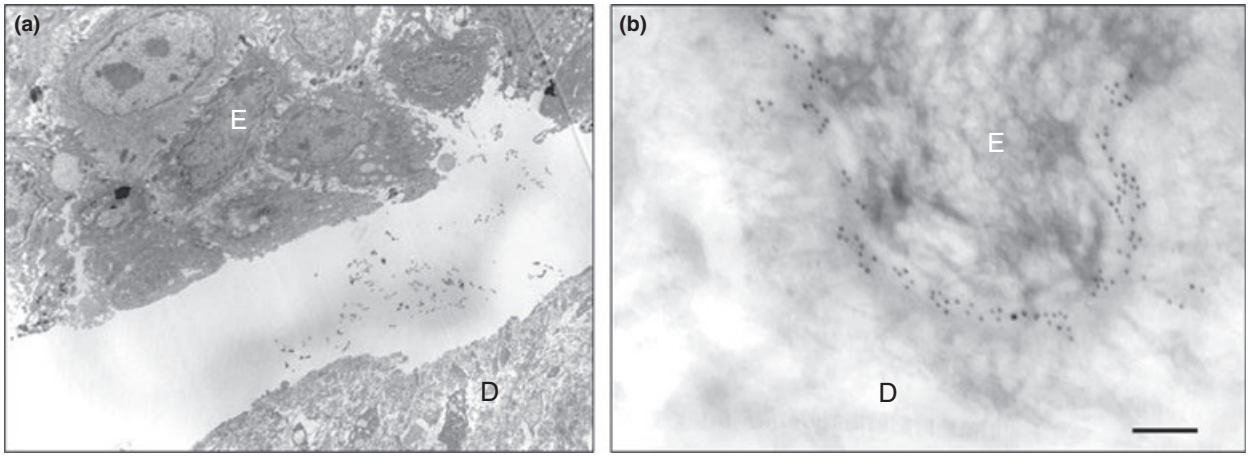

Figure 3. Electron microscopic studies of epidermolysis bullosa acquisita (EBA). Under transmission electron microscopy, lesional skin obtained from a patient with EBA shows a separation below the lamina densa (a). Immunoelectron microscopy using normal human skin reveals immunoreactivity within/below the lamina densa (b). Bars = 200 nm.

dermal–epidermal junction.[68] In rare cases, an additional staining for IgA was described.[44–46,74] Indirect immunofluorescence microscopy using 1 mol/L NaCl-split normal human skin as a substrate demonstrates circulating IgG autoantibodies binding to the dermal side of the artificial split in serum of EBA patients (Fig. 2b,c), which label the sublamina densa zone by indirect immunoelectron

microscopy.[72,75,76] Tissue-bound and circulating antibodies in EBA patients mainly belong to the IgG1 and IgG4 subclasses.[77–80] Wozniak and Kowalewski demonstrated prominent invaginations of the lamina densa and vertically-oriented clumps of anchoring fibrils at and below the dermal–epidermal junction using laser scanning confocal microscopy.[81]

IMMUNOBLOT ANALYSIS

Sera from patients with EBA recognize the 290-kDa protein, or its immunodominant region, the NC1 domain, by immunoblotting with normal human dermal extracts.[22,72] Immunoblot analysis with extracts of human epidermis or cultured keratinocytes and fibroblasts is usually negative (Fig. 2d).[82] A sensitive enzyme-linked immunosorbent assay for the detection of autoantibodies to type VII collagen using recombinant protein is also available.[83]

Some cases of a subepidermal blistering disease with autoantibodies against more than two antigens have been reported. EBA also sometimes complicates other subepidermal autoimmune bullous diseases, for example, against anti-laminin 332, anti-bullous pemphigoid and anti-p-200 antigen.[84–88] At present, clinical features, and histological and immunofluorescence findings are not useful to distinguish between each other. Immunoblot analysis and other molecular biological studies are necessary to further characterize these complicated subepidermal autoimmune bullous diseases. Moreover, the relationship between the antigenic reactivity of these autoantibodies and their prognostic significance needs to be elucidated by more precise analyses.

CLINICAL COURSE AND TREATMENT OPTIONS

Treatment of EBA can often be challenging and primarily consists of systemic corticosteroids, while it remains unsatisfactory, and mainly relies on immunosuppressive agents such as methotrexate, azathioprine or cyclophosphamide.[18–21] Overall, treatment of EBA is difficult, despite the use of corticosteroids combined with other immunosuppressants. Furthermore, long-term immunosuppression has been shown to be associated with increased morbidity and mortality. This includes systemic infections, gastrointestinal disorders, hypertension, osteoporosis, hyperlipidemia, psychiatric disorders, moon face, diabetes mellitus and obesity. Hence, there is a need for the identification of safe and effective alternatives for the treatment modalities of EBA. If required, colchicine or other adjuvants can be added. Some cases of EBA have been identified in which colchicine treatment may be beneficial.[89] This is often used as a first-line management because its side-effects are relatively benign compared with other therapeutic choices. Diarrhea is a common side-effect of colchicine, however, which makes it difficult for many patients to achieve a high enough dose to control the disease. Dapsone has been used in some EBA patients, especially when neutrophils are present in their dermal infiltrate. Recently, i.v. immunoglobulin (IVIG) is one potential promising therapy for patients with EBA, as evidence of its effectiveness and safety is increasing. A number of autoimmune bullous skin diseases have been identified in which IVIG treatment may be beneficial. A review of published work revealed that more than 10 patients with extensive treatment-resistant EBA have – in most cases successfully – been treated.[90–96] Recommended doses are 2 g/kg IVIG monthly until clinical improvement is achieved and no lesions are developed. Because of the limited duration of response retreatment with IVIG (several cycles) is necessary. However, experience with IVIG in patients with autoimmune skin blistering disease is limited. Thus, IVIG is recommended as second-line therapy in autoimmune bullous skin diseases, or for patients not responding to conventional therapy. The mode of action of IVIG in autoimmune diseases including bullous disease, is far from being completely understood. In addition, the most novel treatment is the anti-CD20 monoclonal antibody, rituximab, which is a monoclonal humanized antibody directed against the B-cell-specific cell surface antigen CD20. CD20 is expressed on the cell surfaces of pre-B cells and mature B cells. Rituximab is a chimeric monoclonal anti-CD20 antibody that abolishes these cells through complement- and antibody-dependent cytotoxicity and apoptosis. Thus, rituximab significantly reduces circulating B cells and antibody-producing plasma cells. Rituximab had a dramatic effect on EBA patient in a

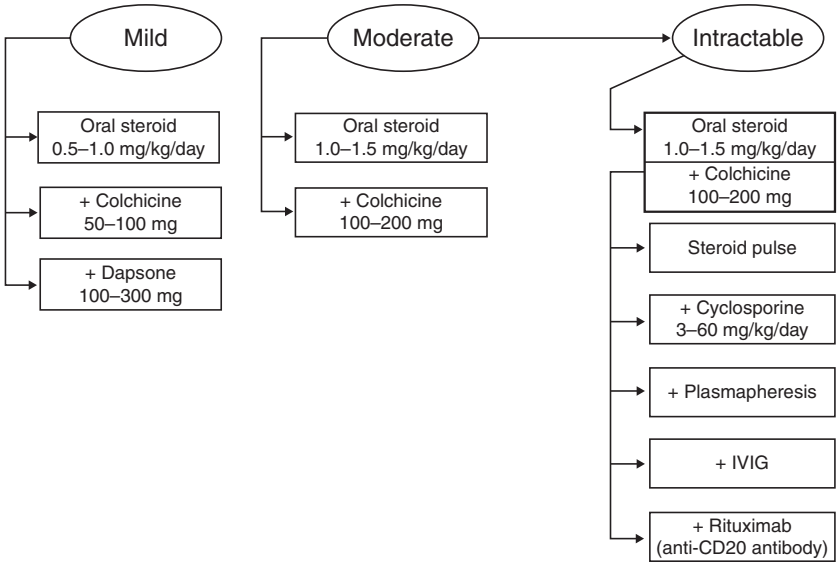

Figure 4. The algorithm for the practice to treat patients with epidermolysis bullosa acquisita (EBA). For the management of EBA, the first-line is of course the use of systemic steroid therapy. Systemic steroid therapy may be a sole treatment in some patients with relatively mild EBA; however, many cases do not respond to this regimen. At present, we fortunately have a variety of other adjuvant regimens available. Among the adjuvant therapies, colchicine is the first choice of treatment; the steroid pulse therapy is the second line of adjuvant therapy. In addition, various immunosuppressive agents may be used in addition to systemic steroid therapy. The effectiveness of these immunosuppressive agents is varied among patients. Intravenous immunoglobulin (IVIG) is considered to be an ideal treatment because it is the only treatment that does not suppress the normal immune activity. The most novel treatment is the anti-CD20 monoclonal antibody rituximab. In the most intractable cases, the combination therapies of these adjuvant treatments may be used with intensive care for severe and possibly fatal infections. Future therapeutic attempts may include the use of monoclonal antibodies able to modulate the immune response (by targeting for example B and/or T cells) or the induction of immunological tolerance by application of peptides or peptidomimetics.

life-threatening situation. In some patients with severe widespread EBA resistant to conventional therapies were successfully treated with rituximab as adjuvant therapy.[97,98] Rituximab is the newest potent therapy in severe and refractory EBA patients. Now, the regimens for these therapies are being examined worldwide. Further data and challenge are needed to establish the real potential of new treatment in EBA. In addition, there are several anti-tumor necrosis factor-α (anti-TNF-α) inhibitors in the class of biological agents (such as infliximab, an anti-TNF-α chimeric monoclonal antibody) that are being considered for use in the treatment of patients with EBA. The algorithm for the practice to treat patients with EBA is shown in Figure 4.

CONCLUSIONS AND PERSPECTIVES

Considerable progress has been made in the last years regarding our understanding of the pathogenesis of EBA. The availability of animal models of EBA provides an important tool to gain further insight into the pathophysiology of the disease. Recently, several new therapeutic agents and modalities have been reported and show promise in the treatment of patients with EBA. The multidisciplinary approach to understanding the mechanisms of central and peripheral tolerance as well as the inflammatory cascade, induced by binding of autoantibodies to type VII collagen, is leading to the more specific therapeutic strategies that counteract the chronic morbidity and mortality of this autoimmune disorder.

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