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Review

Epidermolysis bullosa acquisita: A comprehensive review

Khalaf Kridin[a,*], Diana Kneiber[b], Eric H. Kowalski[b], Manuel Valdebran[c], Kyle T. Amber[b,**]

[a] Department of Dermatology, Rambam Healthcare Campus, Haifa, Israel
[b] Department of Dermatology, University of Illinois at Chicago, Chicago, IL, United States of America
[c] Department of Dermatology, University of California Irvine, Irvine, CA, United States of America

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ABSTRACT

Epidermolysis bullosa acquisita is a rare autoimmune blistering disease which results in vesicle and bullae formation on the skin and erosions on the mucous membranes. EBA is mediated by autoantibodies to collagen VII. Clinically, it can present with numerous phenotypes, though the most common are the mechanobullous and inflammatory variants. Patients with mechanobullous EBA develop non-inflammatory bullae and erosions at sites of trauma while patients with the non-mechanobullous type develop inflammatory lesions which often mimic other blistering conditions including bullous pemphigoid, linear IgA bullous disease, and mucous membrane pemphigoid. Diagnosis is established by having a consistent clinical presentation, DIF, and autoantibodies against collagen VII. In apparent "seronegative" patients, the diagnosis is challenging due to the need for confirmatory tests which are often not routinely accessible outside of the specialized center. In light of EBA's rarity, and lack of any randomized controlled trials, treatment guidelines rely on the small case series presented in the literature. There has been variable success utilizing the arsenal of immunosuppressants and biologics. Development of experimental murine models has facilitated a deeper understanding of EBA's pathogenesis and allows for preclinical testing of numerous novel drug targets predominantly targeting inhibition of neutrophil activation. We herein review the presentation, diagnosis, treatments, and future avenues of research in EBA.

1. Introduction

Epidermolysis bullosa acquisita (EBA) is a rare autoimmune blistering disease (AIBD) which results in vesicle and bullae formation on the skin and erosions on the mucous membranes [1,2]. Based on their clinical presentation, patients can be classified into two main subgroups, a classical or mechanobullous type and an inflammatory or non-mechanobullous type [3,4]. Due to having a similar clinical presentation, EBA was initially described as an adult-onset form of dystrophic epidermolysis bullosa in 1895 [5]. However, following improvement in immunodiagnostics, EBA was categorized as a distinct acquired AIBD [6–8]. EBA is thought to have a genetic predisposition, with an over representation of the HLA-DRB1*15 and HLA-DRB1*16, with a particular association with the HLA-DRB1*15:03 allele in black patients of African descent [9,10]. In contrast to dystrophic epidermolysis bullosa, it can present at any age [10–14].

Autoantibodies to collagen VII bind to the anchoring fibril zone and induce mucocutaneous blistering [6–8,12]. Diagnosis is established by clinical presentation and detection of autoantibodies bound to the basement membrane zone and in the serum against collagen VII [15]. Despite advancements in the understanding of the pathogenesis, effective treatment still remains a challenge. In this review, we seek to provide an integrated overview of the current knowledge of EBA and its management.

Abbreviations: AIBD, autoimmune blistering disease; BMZ, basement membrane zone; BP-EBA, bullous pemphigoid like EBA; BP, bullous pemphigoid; BSLE, bullous systemic lupus erythematosus; COLVII, collagen VII; CP-EBA, cicatricial pemphigoid; DEJ, dermal epidermal junction; DIF, direct immunofluorescence; EBA, epidermolysis bullosa acquisita; FcγRIV, Fcγ receptor IV; Flii, flightless I; FOAM, fluorescence overlay antigen mapping; IA, immunoabsorption; IB, immunoblot; IBD, inflammatory bowel disease; IEM, immunoelectron microscopy; Ig, immunoglobulin; IgA-EBA, LABD like EBA; IIF, indirect immunofluorescence; ISA, immunosuppressant; IVIg, intravenous immunoglobulin; LABD, linear IgA bullous disease; MAPK, mitogen associated protein kinase; MM-EBA, mucous membrane like EBA; MMF, mycophenolate mofetil; NKT, natural killer T-cell; MMP, mucous membrane pemphigoid; PDE, phosphodiesterase; PI3Kδ, phosphatidylinositol-3-kinase δ; ROS, reactive oxygen species; sCD32, soluble CD32; SSS, salt split skin; TNF, tumor necrosis factor

* Correspondence to: K. Kridin, Department of Dermatology, Rambam Health Care Campus, POB 9602, Haifa 31096, Israel.
** Correspondence to: K. T. Amber, Department of Dermatology, University of Illinois at Chicago, 808 S Wood St, RM377, Chicago, IL 60612, United States of America.
E-mail addresses: dr_kridin@hotmail.com (K. Kridin), ktamber@uic.edu (K.T. Amber).

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2. Epidemiology and associations

The incidence of EBA is thought to be between 0.08 and 0.5 new cases per million people per year, affecting males and females equally [11,12,16–19]. EBA may be acquired at any age, with a median age of 50 years, and peaks of onset in the first three decades and the seventh and eighth decades of life [11,12]. Non-mechanobullous forms comprise the majority of EBA cases (55%), followed by mechanobullous form (38%) and forms with characteristics of both (7%) [12]. EBA is estimated to affect 1 in 18 patients with sub-epidermal autoimmune blistering disease with a small portion of patients reported as having concurrence of other AIBDs such as bullous pemphigoid (BP), mucous membrane pemphigoid (MMP), p200 pemphigoid, paraneoplastic pemphigus, and pemphigus vulgaris [12,15,19]. In a recent meta-analysis, 9.6% of patients were found to have comorbid conditions [12]. Of these patients, 4.4% had associated inflammatory diseases with Crohn's disease, ulcerative colitis, another AIBD, thyroiditis, psoriasis, and rheumatoid arthritis occurring most frequently [12]. ANA positivity was also found in 20% of patients [12]. Although rare, acquired hemophilia A has been seen complicating EBA in 5 cases [20].

The association of EBA with inflammatory bowel disease (IBD) has been a topic of interest for over 30 years [21,22]. Patients with EBA often develop gastrointestinal erosions and scarring in the oral, laryngeal, and esophageal mucosa; regions which are commonly affected by IBD [12,23–26]. Furthermore, recent studies propose that IBD occurs in 1.5% of patients with EBA, with Crohn's disease occurring more frequently than ulcerative colitis [12,27]. In the majority of cases, IBD is diagnosed prior to the onset of EBA [28]. However the source of their relation is still to be determined. Full-length collagen VII is present in the basement membrane of colonic mucosa and autoantibodies to the protein have been found in the sera of 68% of patients with Crohn's disease and ulcerative colitis in one study [27]. However, these serum collagen VII autoantibodies were unable to bind to the dermal-epidermal junction (DEJ) of human skin, possibly due to having different antigenic epitopes [27]. It is possible that inflammation and damage to the colonic mucosa from IBD may expose the immune system to previously masked collagen VII, resulting in autoantibodies, which in some patients can epitope spread to pathogenic epitopes [28]. Additional studies are needed to further clarify this relationship between IBD and EBA.

3. Mechanism

EBA is characterized by the loss of tolerance and subsequent development of autoantibodies against collagen VII [29–31]. Collagen VII forms the main component of anchoring fibrils in the hemidesmosomes found in the sub-lamina densa of the skin and mucous membranes [12,32,33]. The 290 kDa protein consists of a central collagenous domain flanked by two non-collagenous domains, NC1 and NC2 [34,35]. Autoantibodies targeting both NC1 and NC2 domains are seen in EBA, with NC1 forming the dominant epitope [29–31,35]. Autoantibodies bind to affected tissue at the DEJ of the skin, esophageal mucosa, and conjunctival mucosa [30,36,37]. In the serum, immunoglobulin (Ig) G autoantibodies to collagen VII are observed most commonly, but IgA, IgM, and IgE have also been detected [12]. Serum IgG binds to the DEJ and recruits leukocytes to the region in a dose-dependent manner [38]. Higher concentrations of IgG result in a larger separation of the DEJ [38]. Serum IgE to collagen VII also binds to the basement membrane zone (BMZ) and is elevated in the serum of patients with EBA, similar to findings in patients with BP, though its pathogenicity is unclear [39].

Experimental mouse models further support the hypothesis that autoantibodies binding to collagen VII initiate an inflammatory pathway that leads to blister formation [40,41]. Passive transfer of antibodies to collagen VII activate the complement system [42]. Pro-inflammatory cytokines are then released, and neutrophils are drawn to the skin [40]. Immune complex formation also activates natural killer T (NKT) cells and γδ-T cells, which further attract neutrophils into the area [41]. Immune complexes bind to Fcγ receptor IV (FcγRIV) on neutrophils, leading to the release of reactive oxygen species (ROS) and proteolytic enzymes, whereby inducing blister formation [40,43,44]. Flightless I (Flii), a cytoskeleton remodeling protein, is also believed to contribute to the destabilization of the DEJ through its interactions with transforming growth factor (TGF) β [45,46]. TGF-β increases collagen 7 mRNA expression by way of its downstream effect on the collagen VII gene, *COL7*, promoter regions [47–49]. EBA models of mice over-expressing Flii show increased sub-epidermal blistering, whereas in mice with reduced expression of Flii formation of blisters was impaired [45,46]. Alterations in the Flii-TGF-β pathway may consequently lead to reduced collagen VII and predispose patients with collagen VII autoantibodies to more severe skin disease [47–49]. The effect of Flii on the inflammation mediated skin blistering has not yet been determined in human studies.

4. Clinical manifestations

In the mechanobullous disease variant, skin fragility and blister formation occur with residual scarring and milia production on extensor surfaces of the skin and sites prone to trauma [2]. Lesions tend to be encompassed by noninflamed skin, in contrast to non-mechanobullous types which often present with erythematous or urticarial skin [15]. Nail dystrophy and scarring alopecia can also be observed [15]. Mild cases of mechanobullous type present similarly to porphyria cutanea tarda with more severe cases appearing like dystrophic epidermolysis bullosa [2,50,51].

In non-mechanobullous types, widespread lesions with vesicles and bullae are found on the trunk, flexural, and intertriginous areas [1]. In contrast to mechanobullous types, inflammation and urticaria are present and lesions often resolve without scarring and formation of milia [1,15]. These variants frequently mimic other blistering conditions such as BP, P200 pemphigoid, linear IgA bullous dermatosis (LABD), or MMP [1,15,52–55].

Several subcategories of EBA phenotypes have been described. The term BP-like EBA (BP-EBA) has been proposed for patients who have a generalized eruption of vesicles and bullae on the extremities and trunk, which may be pruritic and erythematous [1,4]. The presentation of BP-EBA and BP is often so indistinguishable that up to 10–15% of patients who presented prior to the advent of newer diagnostic tests, may have been misdiagnosed with BP instead of EBA due to the near identical presentation of these conditions and the presence of linear IgG on direct immunofluorescence [1,56–58]. However, skin fragility, bullae on normal skin, milia, and involvement of the face or extensor surfaces should point the clinician to EBA rather than BP [15]. Another presentation is LABD-like EBA (IgA-EBA), where patients present with linear IgA deposits in the BMZ on direct immunofluorescence (DIF) and often improve with dapsone therapy [52,59,60]. A localized variant reminiscent of Brunsting-Perry cicatricial pemphigoid (CP-EBA) presents with cicatrizing involvement of the scalp, neck and shoulders with non-healing erosions [1,15,61,62]. CP-EBA often has involvement of the mucous membranes distinguishing it from Brunsting-Perry cicatricial pemphigoid [61,63]. Patients who present with predominantly mucous membrane involvement are categorized as having mucous membrane pemphigoid-like EBA (MM-EBA) [1,64]. MM-EBA can affect mucous membranes lined by squamous epithelium, including the mouth, pharynx, esophagus, conjunctiva, anus and genitalia [1,12].

Mucosal involvement occurs in 23% of patients with EBA, with oral lesions occurring most frequently followed by ocular, genital, esophageal, tracheal/laryngeal, and anal lesions [1,12]. Complications resulting from ocular involvement include conjunctival blistering, symblephara formation, and trichiasis [23,24]. Likewise, esophageal erosions, strictures and stenosis are found on endoscopy and can significantly affect the quality of life of patients with EBA [24,36]. Other manifestations include atrophic scarring, hypopigmentation, nail

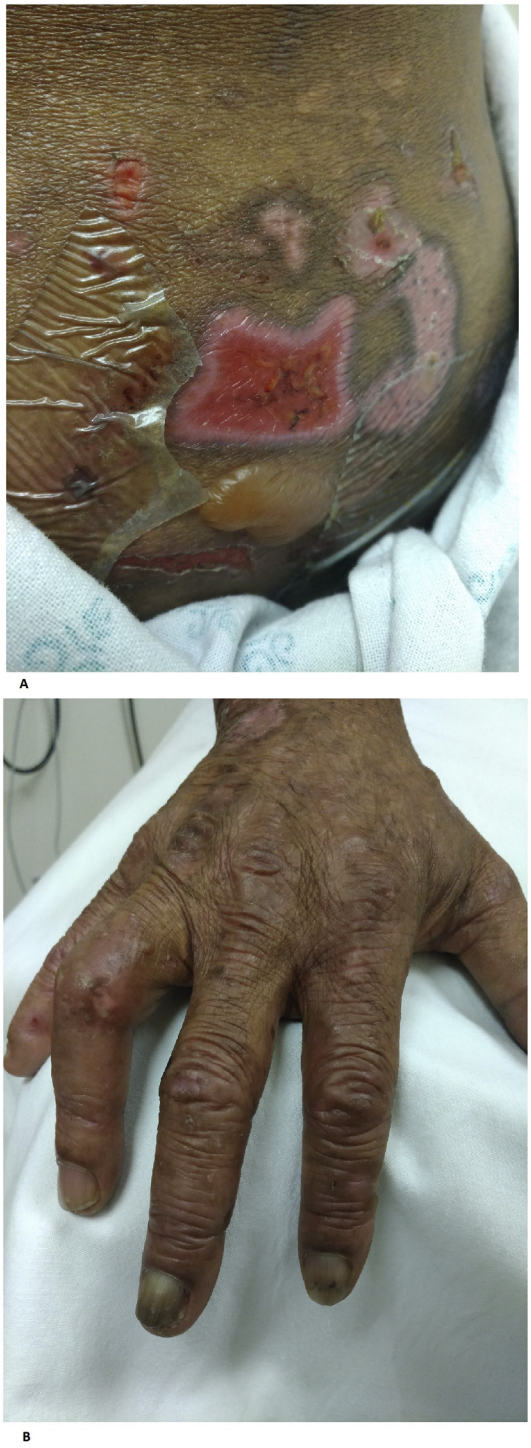

Fig. 1. Epidermolysis bullosa acquisita. A) Tense bulla forming at a site of adhesive application with early scar formation. B) Dorsal hand erosions overlying joints with milia formation.

dystrophy, anonychia, and hand deformities [1,23,24,65]. A clinical photograph of a patient with the mechanobullous variant developing at a site of adhesive dressing and a more characteristic location on dorsal hands with milia formation is presented in (Fig. 1a) and (Fig. 1b) respectively.

5. Diagnosis

The diagnosis of EBA requires several tests in order to confirm the diagnosis [15,66]. The various techniques used to diagnose it, as well as formal diagnostic criteria are discussed below.

5.1. Histopathology

Histopathological findings observed in EBA include subepidermal blister formation which classically courses with none or little inflammation [65]. Nevertheless, the degree of the infiltrate may vary and present with a mixed inflammatory infiltrate with variable number of eosinophils. In fact, Barreiro-Capurro et al. found that inflammatory EBA was the most common variant in their series that included 9 EBA cases [67]. Because histological findings observed in inflammatory variants of EBA may be indistinguishable from those seen in other immunobullous disorders, especially bullous pemphigoid (BP), immunofluorescence and other testing are required for definitive diagnosis [65,68]. Histology from a case of mechanobullous EBA is shown in (Fig. 2a).

5.2. DIF + DIF serration

Routine DIF microscopy of perilesional skin shows a linear immune deposit pattern along the cutaneous BMZ, similar to that seen in different sub-epidermal AIBDs (Fig. 2b) [58]. IgG and C3 are most commonly observed but IgA or IgM can also be seen [19,69–72]. Serration analysis can allow further differentiation of sub-epidermal immunoglobulin deposition. A u-serrated pattern can be seen on DIF which is exclusive to EBA and bullous systemic lupus erythematosus (BSLE). U-serration differentiates these patients from those with BP, MMP, LABD, p200 pemphigoid, and anti-laminin 332 pemphigoid with up to 100% specificity [58]. The pattern is formed by autoantibodies binding to collagen VII as a part of the anchoring fibrils below the lamina densa forming a u shape [58,73]. In one study, serration pattern analysis revealed three times more EBA patients, who without serration analysis, would have been undetected due to negative serology [63]. This method is not widely utilized, however, it can be easily learned *via* pictorial instruction [15,74].

5.3. IIF, IIF with SSS, IIF with collagen VII deficient skin

On indirect immunofluorescence (IIF), deposition of autoantibodies on the BMZ of intact skin is observed [7]. This is identical to that seen in other sub-epidermal bullous diseases. [75] IIF on salt split skin (SSS) shows binding of autoantibodies on the dermal side in patients with EBA which helps distinguish these patients from patients with BP or some types of MMP [75–78]. IIF on SSS has a sensitivity of 74.7% and specificity of 99% [79]. A limitation of this test is that patients with anti-laminin 332 and anti-p200 pemphigoid also show binding on the dermal side of SSS [9,58]. Sera from patients with EBA is unable to stain collagen VII deficient skin using IIF which can be an additional helpful tool if available [80]. DIF showing u serration pattern can also differentiate EBA from the n-serration pattern of anti-p200 pemphigoid and anti-laminin-332 [9,58]. Differentiation of EBA from BSLE requires clinical pathologic correlation.

5.4. Elisa

Multiple ELISA assays have been developed to detect collagen VII autoantibodies [31,81,82]. Depending on the epitope used, the sensitivity and specificity can significantly vary with sensitivities ranging from 30% to 97.9% when both the NC1 and NC2 domain are used [79,82,83]. Caution, however, must be used in interpreting the upper level of sensitivities, as known seropositive patients (IIF, ELISA, or western blot) were pre-selected. ELISA is only sensitive in 23% of SSS-negative cases, with a prospective sensitivity of 45% [82,84].

Quantitative analysis of serum anti-collagen VII IgG antibodies has also been found to correlate with clinical disease severity [79,85–87].

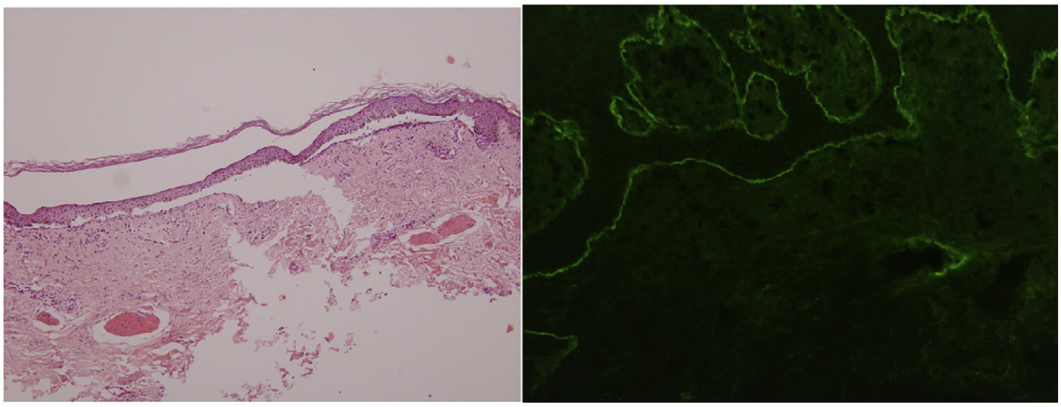

Fig. 2. Epidermolysis bullosa acquisita. A) Subepidermal blister containing sparse inflammatory cells. H&E x 40. Courtesy of Dr. Ruzeng Xue, Southern Medical University, Guangzhou, China. B) Direct immunofluorescence shows linear deposition of IgG at the dermoepidermal juction. DIF x 200. Courtesy of Dr. Ruzeng Xue, Southern Medical University, Guangzhou, China.

One drawback however, is that ELISA has limited sensitivity in patients with low titers of anti-collagen VII antibody or when the patient has autoantibodies to an epitope not recognized by that particular ELISA assay [84]. Another possible pitfall when using ELISA is that patients with IBD, BP, pemphigus vulgaris and BSLE may also have anti-collagen VII autoantibodies in their serum resulting in false positives [27,31,77,88,89].

A new ELISA assay was recently developed comprising of recombinant forms of desmoglein 1, desmoglein 3, envoplakin, BP180, BP230, and NC1 domain of collagen VII [90]. In addition to allowing for faster diagnosis of patients presenting with new AIBD, the multivariant assay has high sensitivity and specificity though again these patients were preselected seropositive patients [90].

5.5. IIF on biochip with NC1 COL7 transfected human cells

IIF on biochip with *NC1 COL7* transfected cells is a novel technique for detection of autoantibodies to collagen VII in the sera of patients with EBA [91]. Human cell lines (HEK293) expressing the NC1 domain of collagen VII are used, and substrates are applied to glass slides and cut into small fragments forming biochips. The biochip is then incubated with serum samples, and immunofluorescent staining with anti-human antibodies is used. IIF on biochip is as efficacious and costs 50% less than ELISA [91]. The sensitivity and specificity are comparable to NC1/NC2 ELISA. Nonetheless, the sensitivity is lower when compared to full-length collagen VII ELISA [82].

5.6. Fluorescence overlay antigen mapping

Fluorescence Overlay Antigen Mapping (FOAM) is a useful technique for differentiating EBA from other sub-epidermal bullous disorders. By using routine immunofluorescence microscopy it is more affordable and faster than electron microscopy [92]. Using IF and perilesional skin from patients with EBA, digitized color images are formed by staining lamina lucida IgG deposits one color, against collagen VII, a different color. In patients with EBA there is an overlap of the fluorescence whereas in patients with BP, for example, the two stains are seen to be separate [80,92].

5.7. IEM or direct IEM

With immunoelectron microscopy (IEM), deposition of IgG beneath the basal lamina in the dermis of perilesional skin is visualized [7]. Using direct IEM, binding of autoantibodies to collagen VII in a u-shaped pattern is displayed, resembling upstanding arms between the rootlets of the basal keratinocytes [58]. In contrast, autoantibodies in other sub-epidermal AIBD form n-shape patterns due to the binding of hemidesmosomes on the plasma membrane of basal keratinocytes [58].

5.8. Immunoblot

Immunoblot (IB) assay using human dermal extract detects autoantibodies to the 290 k-Da collagen VII NC1 protein in the serum of patients with EBA [93]. This test is useful in discriminating between patients with p200 pemphigoid who have similar findings on IIF with SSS [19]. However, like ELISA, patients with IBD and BSLE who have autoantibodies to collagen VII in their serum may also be picked up [27,77,88]. Likewise, a portion of patients with EBA have IgA autoantibodies only and may not be picked up on an IB IgG assay [52].

5.9. Collagen IV immunohistochemistry

Collagen IV, a lamina densa protein, stains above the blister cavity in patients with EBA on immunohistochemistry [94,95]. Staining below and above and below the blister in EBA may also be seen but less commonly. This helps to differentiate from patients with BP, LABD, and p200 pemphigoid who more commonly have staining of collagen IV at the base [94–96]. A limitation of this method is that patients with BSLE may also have staining at the roof of the blister [94].

5.10. International bullous disease group criteria for diagnosis

In 2017, the International Bullous Disease Group developed diagnostic criteria for EBA (Table 1) [15]. They reached agreement that routine histopathology, DIF, and IIF, although widely available, cannot alone distinguish between the various sub-epidermal AIBDs. The diagnosis of EBA should then be confirmed by EM or direct IEM, serration pattern analysis by DIF, FOAM, ELISA, IIF on BIOCHIP with *NC1 COL7* transfected human cells, immunoblotting, IIF on skin deficient in collagen VII, and/or indirect IEM. They proposed that the ideal steps to diagnosis would be a clinical presentation consistent with EBA [1], subepidermal blister on histology (2, optional), a positive DIF showing linear IgG, C3, IgA and/or IgM deposits within the BMZ [3], and an ELISA with collagen VII autoantibodies [4]. If [1] [4] are consistent then no further testing is necessary for confirmation. If ELISA is not available, a highly probable diagnosis of EBA can be established if the clinical presentation [1] and DIF [3] are consistent, and one of the following can demonstrate anti-COLVII autoantibodies: positive indirect immunofluorescence [4], positive immunoblot, or IIF on collagen VII deficient skin is negative [5].

Table 1
Diagnostic criteria of epidermolysis bullosa acquisita (adapted from International Bullous Disease Group Diagnostic criteria for the diagnosis of EBA) [15].

International bullous disease group diagnostic criteria for the diagnosis of EBA
Diagnosis is highly probable if:
(1) Bullous disorder consistent with EBA
AND
(2) Histopathology displaying sub-epidermal blistering (Optional)
AND
(3) Positive DIF of perilesional skin with linear IgG, C3, IgA, and/or IgM deposits along the BMZ
AND
(4) Circulating autoantibodies against collagen VII by ELISA or IIF on collagen VII expressing human cells
OR
(5) Labeling of the anchoring fibrils by indirect IEM or negative IIF on collagen VII deficient skin
For seronegative patients, diagnosis is definitive if (1) AND (3) is present AND 1 or more of the following:
(6) U-serration pattern on DIF
OR
(7) Direct IEM of perilesional skin with immune deposits in the anchoring fibril zone +/− the lower lamina densa
OR
(8) FOAM with *In vivo* bound immune deposits below type IV collagen
If (6)- (8) are not available for testing, the diagnosis is possible if (1) AND (3) are present
AND:
(9) Dermal labeling of DIF and/or IIF on SSS

For patients who are seronegative and do not have anti-collagen VII autoantibodies, a modified approach was developed [15]. To definitively diagnose the patient with EBA, the clinical presentation [1] and DIF should be consistent [3] as above, then at least one of the following is needed: u-serration pattern on DIF [6], direct IEM displaying immune deposits at the anchoring fibril zone [7], or FOAM demonstrating immune deposits below collagen VII [8]. These tests are often found in academic centers and are not readily available to general dermatologists. If these diagnostic tests are not accessible, DIF and/or IIF on SSS [9] can be performed, although, patients with anti-laminin-332 pemphigoid or p200 pemphigoid can be misdiagnosed [9,58]. The diagnosis can then be confirmed in seronegative patients by exclusion of autoantibodies against laminin 332 and the p200 chain. No consensus was reached about which test would be applicable worldwide. It was determined that the tests chosen by the practitioner will likely be based on the clinical presentation of the patient, the geography of the practitioner and the accessibility of the diagnostic tests.

6. Treatment

Treatment of EBA presents a unique challenge clinically because of its low prevalence, and lack of any randomized controlled trials. Therapeutic options come in tiered recommendations from a consensus of experts in AIBD [65]. However, it is evident from the plethora of case reports and therapeutics utilized that each patient's regiment has to be individualized accounting for any comorbidities, potential toxicities, and predisposition to adverse effects from these medications. General education regarding their disease should be provided to all EBA patients. In particular therapeutic measures to prevent any trauma induced blistering and wound management should be provided to prevent disease progression or possible infection. Although the mechanobullous subtype has been noted to be resistant to conventional steroid and immunosuppressive treatments we do not make a distinction between these two overarching subtypes when discussing therapeutic options below.

6.1. Neutrophil targeting therapies

Several drugs targeting neutrophil function have been utilized in the treatment of EBA. Treatment regimens have involved colchicine as part of a combination first line therapy, as an adjuvant to allow for steroid tapering, and as monotherapy [52,97,98]. Therapeutic responses were noted as early as two weeks on initial dosages between 0.5 and 2.0 mg/day with titration up to a dosage that avoided any adverse effects. Although, colchicine is well tolerated, it has notable gastrointestinal side effects, such as abdominal pain and diarrhea, and thus should be used cautiously in patients with concomitant IBD [99,100]. Maintenance dose colchicine was maintained for several months in most reported cases, either as monotherapy or in addition to immunosuppressives [98,101,102]. Notably, while on colchicine monotherapy one patient exhibited a decrease in pathogenic, anti-collagen VII, antibodies suggestive of colchicine acting through inhibition of antibody secretion by plasma cells [98].

Dapsone is an additional neutrophil targeting therapy particularly useful in the inflammatory subtype of EBA. Similarly, to colchicine, dapsone was often part of a treatment regimen including steroids and titrated up appropriately. Starting doses were between 25 and 50 mg/day with patients taking up to 150 mg/day during active treatment and many continuing with a lower maintenance dose for several months [52,103,104]. When combined with systemic corticosteroids, dapsone has proven particularly effective in the treatment of pediatric EBA [101,105,106].

Minocycline has been an effective adjuvant treatment in several AIBD. Its pathomechanism is believed to center on inhibition of granulocyte migration and cytokine production [107]. Its use in EBA however, is limited to one case that was resistant to treatment with prednisolone and cyclosporine and required a therapeutic adjustment due to severe adverse effects from diaphenylsulfone [107]. 200 mg/day of minocycline allowed for tapering of prednisolone and prevented disease progression.

6.2. Conventional Immunosuppressives

The use of immunosuppressive agents such as mycophenolate mofetil (MMF) which suppresses T and B cell proliferation has shown guarded success in the treatment of recalcitrant EBA [108,109]. When used as a corticosteroid sparing agent, MMF at dosages between 2 and 3 g/day showed a clinical response between 2 and 4 months and allowed for complete cessation of steroid use in most patients. However, in order to remain in remission all patients have required a maintenance dose of MMF, with some being unable to taper off steroids completely or requiring adjuvant plasmapheresis [110,111]. Two case reports have demonstrated disease control using cyclosporine at a dose of 5 mg/kg, even in cases of severe mucosal and upper airway involvement [112,113].

6.3. Intravenous immunoglobulin and rituximab

EBA is often recalcitrant to the above therapies, following a chronic course, often with significant difficulty in weaning off of corticosteroids. Cases of treatment resistant EBA have been widely shown to be responsive to intravenous immunoglobulin (IVIg) infusions [114,115]. Its postulated mechanism of action in antibody mediated autoimmune diseases centers on its autoantibody neutralizing properties and saturation of the FcRn receptor which stimulates antibody catabolism [116,117]. IVIG additionally leads to numerous other immunoregulatory mechanisms that can treat AIBD [118,119]. Individual cases report on exhausting most known therapeutic treatments for EBA, such as corticosteroids, methotrexate, dapsone, plasma exchange, azathioprine, cyclosporine, colchicine, and cyclophosphamide, prior to resorting to IVIg. Clinical improvement was often noted after 2–4 cycles of 2 mg/kg/cycle and any adjuvant treatment was often tapered and

discontinued [114,115,120,121]. In the largest study to date, Ahmed et al. showed a complete clinical response in 10 patients with previously recalcitrant EBA. Patients received an average of 23.1 [16–31] infusion cycles over 38.8 [30–52] months. Any previous treatments were tapered off and discontinued over a 5–9 months period allowing for IVIg monotherapy. New lesional development was noted with less frequent infusions. However, instead of utilizing corticosteroids an additional infusion cycle was typically given. After cessation of IVIg all patients remained in remission through their follow up, with a mean of 53.9 [29–123] months [122].

Rituximab, a CD-20 monoclonal antibody, has been trialed in a small number of EBA patients [123]. Currently, two established protocols are used, the lymphoma protocol consisting of 4 weekly infusions of 375 mg/m^2, and the rheumatoid arthritis protocol of two 1000 mg infusions separated by 14 days [65]. Akin to IVIg, rituximab was often initiated after trials of multiple conventional immunosuppressant (ISA) drugs [124,125]. In a recent case series, Bevans et al. highlighted the effectiveness of combination treatment including dapsone, mycophenolate, corticosteroids and rituximab in achieving complete disease control in 2 patients [125]. Treatment response was noted 2–3 months after initiation of rituximab. Although, one patient was able to discontinue all treatment, 2 out of 3 patients required a maintenance dose of ISAs [125]. Rituximab has also been combined successfully with immunoabsorption (IA) or IVIg [124,126]. This combination of rituximab-IA effectively depleted the B-cell population in both patients but exhibited divergent results on grounds of clinical improvement and depletion of pathogenic antibody titers [124]. Based on similar principles of rapid auto-antibody depletion, and maintenance of remission with rituximab, Oktem et al. showed significant improvement based on the Autoimmune Bullous Skin Disorder Intensity Score. Long term results however are unavailable as 4 of 5 patients continued receiving regular IVIg infusions [126].

7. Introduction to the EBA mouse

Due to the relative scarcity of EBA patients, an understanding of its pathogenesis and identification of potential therapeutic targets has been greatly aided through the development of animal models. Two main mouse models exist, the passive antibody transfer and the active immunization induced model. Transfer of isolated anti-collagen VII antibodies from EBA patients did not yield consistent results. EBA patient sera does not show consistent reactivity to murine skin, and complement binding potential when bound [127,128]. Human and murine collagen are sufficiently different that patient autoantibodies may recognize different epitopes or not activate the complement and neutrophil cascade sufficiently to induce blistering [127]. Hence the current transfer model utilizes isolated IgG against murine collagen VII from immunized rabbits. Conversely, the immunization induced model allows for investigation of the loss of tolerance to collagen VII and the generation of the autoantibody response. Generation of a recombinant murine collagen VII NC1 domain, and immunization of mice with this isolate results in detectable autoantibody production and subepidermal blistering consistent with EBA [129,130].

Several mechanistic aspects of EBA have been validated utilizing mouse models, such as the pathogenicity of anti-collagen VII antibodies, their role in complement activation and leukocyte extravasation [29,127,128]. Because these models replicate the inflammatory subtype, presumably their effects will be best realized in that patient cohort. These *in vivo* models offer the possibility of studying further treatments and pathomechanisms which may improve the treatment of EBA.

7.1. Methylprednisolone

While corticosteroids are often used to manage EBA, the specific mechanism by which they exerted effect was not previously entirely clear. Methylprednisolone hindered immune cell activation of neutrophil degranulation, ROS production, and autoantibody induced blister formation at the DEJ [131]. Furthermore, Hellberg et al. noted significant decreases in downstream effector molecules Akt, ERK1/2, and p38 mitogen associated protein kinase (MAPK) with methylprednisolone treatment. These signaling molecules were then individually investigated using selective inhibitors. Results indicated that inhibition of all 3 pathways hampered ROS production but only p38MAPK inhibition affected neutrophil degranulation [131]. Results were further verified on a passive transfer mouse model that showed significant decreases in body surface area involved [131].

7.2. Calcitriol

Studies have identified increased levels of autoimmune diseases in patients with hypovitaminosis D [132]. Although the immunomodulatory role of vitamin D has not been fully clarified, Tukaj et al. showed significant effects of oral calcitriol administration in both passive transfer and active immunization mouse models. Neutrophil chemoattraction by key immune effectors cells, Gr-1 + myeloid cells, and activation was hampered with oral calcitriol [133]. Compared with controls, mice which received prophylactic calcitriol had a lower body surface area affected, and histologically demonstrated a weaker dermal infiltration of neutrophils [133].

7.3. PI3K inhibitors

Immune complex mediated neutrophil activation results in downstream kinase activity involved in development of EBA in mouse models. Specifically, studies have identified impaired production of ROS and protection from blistering in mice deficient in phosphatidylinositol-3-kinase δ (PI3Kδ) [134]. In a follow up study, Koga et al., utilizing LAS191954, a novel PI3Kδ inhibitor, showed clinical improvement and regression in disease in a dose dependent fashion [135]. When compared to controls, the circulating IgG anti-collagen VII antibody levels and dermal infiltrate did not differ. PI3Kδ inhibition's therapeutic effects hinder on the kinase's role in the downstream effects of myeloid cell activation and the oxidative burst rather than on autoantibody production [135]. Furthermore, this novel compound displayed similar effects to high dose methylprednisolone in the inhibition of immune cell mediated ROS release and may serve as a viable alternative in the future [131].

7.4. Tumor necrosis factor-α inhibition

Tumor necrosis factor (TNF) α is a known chemoattractant for neutrophils, and its overexpression in AIBD has been established [136,137]. Hirose et al. showed elevated levels of TNF-α expression in lesional and perilesional tissue, and a lesion to serum gradient in EBA patients and mouse models [138]. Treatment with a TNF-α antibody, as well as use of etanercept in established EBA mice, showed a reduction in blistering and slower disease progression. Of note, this study established the role of macrophages in initiating ROS and blister production. TNF-α inhibition resulted in reduced numbers of lesional macrophages [138]. Although development of clinical disease was not halted in these mouse models, the role of TNF-α, and its inhibition present a unique therapeutic target for which several selective antibodies exist.

7.5. Phosphodiesterase 4 inhibitors

Inhibition of phosphodiesterase (PDE) 4 has been shown to decrease levels of pro-inflammatory cytokines, and increase expression of anti-inflammatory ones, such as IL-10 [139]. Furthermore, select PDE4 inhibitors have been shown to inhibit matrix metalloproteinase (MMP) 9 activity which is essential in blister development [140]. Koga et al. identified significantly increased expression of PDE4 in inflammatory

type EBA patient lesions relative to patients with the mechanobullous subtype and healthy controls [141]. Several PDE4 inhibitors were shown to decrease markers of neutrophil activation and impede disease progression in active immunization mouse models. Levels of autoantibodies did not differ significantly from control mice, indicating that PDE4 inhibitors therapeutically target neutrophil activation [141]. The inhibition of PDE4 has proved fruitful in animal models of EBA through reduced activation of neutrophils, and a shift from the inflammatory cytokine state.

7.6. Intravenous immunoglobulins

Although IVIg is already an established treatment alternative in recalcitrant or severe EBA, the mechanism through which it exacts its therapeutic effect remains unclear. Through testing IVIg as monotherapy in mouse models, Hirose et al. showed that it exerts change in the adaptive as well as innate immune systems. IVIg treated mice were found to have significantly lower levels of anti-collagen VII antibodies and in general a shift towards non-complement fixing antibodies. Complement fixation and receptor activation of neutrophils have been implicated in tissue injury in EBA. [44,142] By highlighting the lower intensity of C3 deposition at the DEJ, reduced expression of FcγIV in peripheral myeloid cells, and histologically milder disease and dermal neutrophil infiltration, their study demonstrates the multifaceted mechanisms by which IVIg exerts its effect [143].

7.7. Inhibition of neutrophil activation

Kasperkiewicz et al. has identified the FcγIV receptor as the only required receptor on the surface of neutrophils to induce tissue damage [44]. Through competitive inhibition of FcγIV-immune complex interaction at the DEJ, soluble CD32 (sCD32) was shown to inhibit blister formation and FcγIV dependent ROS release from neutrophils [144]. Additionally, sCD32 treatment decreased circulating anti- collagen VII antibodies however, the mechanism behind this remains speculative. Mice deficient in FcγIV have been shown to be resistant to blister development [44]. Inhibition of neutrophil interaction with immune cells by Iwata et al. showed a significant effect on disease severity by modulation of antibody production and inhibition of neutrophil dependent injury [44].

8. Conclusion

EBA is an AIBD that has a diverse array of clinical presentations which can have a devastating impact on patients. Properly diagnosing EBA is often a challenge, as many diagnostic technologies are limited to specialized labs. Due to its rarity, clear treatments guidelines, especially for the various phenotypic presentations, are not readily available. The presence of a mouse model, however, allows for *in vivo* studies that will hopefully allow for improvement in the treatment of EBA.

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