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GUIDELINES

S2k guidelines on diagnosis and treatment of linear IgA dermatosis initiated by the European Academy of Dermatology and Venereology

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Abstract

Introduction: Linear IgA dermatosis (LAD) is a rare subepidermal autoimmune bullous disease (AIBD) defined by predominant or exclusive immune deposits of immunoglobulin A at the basement membrane zone of skin or mucous membranes. This disorder is a rare, clinically and immunologically heterogeneous disease occurring both in children and in adults. The aim of this project is to present the main clinical features of LAD, to propose a diagnostic algorithm and provide management guidelines based primarily on experts' opinion because of the lack of large methodologically sound clinical studies.

Methods: These guidelines were initiated by the European Academy of Dermatology and Venereology (EADV) Task Force Autoimmune Bullous Diseases (AIBD). To achieve a broad consensus for these S2k consensus-based guidelines, a total of 29 experts from different countries, both European and non-European, including dermatologists, paediatric dermatologists and paediatricians were invited. All members of the guidelines committee agreed to develop consensus-based (S2k) guidelines. Prior to a first virtual consensus meeting, each of the invited authors elaborated a section of the present guidelines focusing on a selected topic, based on the relevant literature. All drafts were circulated among members of the writing group, and recommendations were discussed and voted during two hybrid consensus meetings.

Results: The guidelines summarizes evidence-based and expert opinion-based recommendations (S2 level) on the diagnosis and treatment of LAD.

Conclusion: These guidelines will support dermatologists to improve their knowledge on the diagnosis and management of LAD.

Frédéric Caux and Aikaterini Patsatsi shared first co-authorship.

For Affiliation refer page on 1018

INTRODUCTION

Linear IgA dermatosis (LAD) is a rare subepidermal autoimmune bullous disorder (AIBD) defined by predominant or exclusive immune deposits of immunoglobulin A (IgA) at the basement membrane zone (BMZ) of skin or mucous membranes. This disorder is a rare, clinically and immunologically heterogeneous disease occurring both in children and in adults. It may develop spontaneously or be drug-induced. LAD was first differentiated from bullous pemphigoid (BP) and dermatitis herpetiformis (DH) in 1976 by Jablonska et al.[1] The same group demonstrated that some children have a blistering disease with continuous IgA deposits along the BMZ which was neither BP, nor DH and introduced the term linear IgA dermatosis of childhood, also known as chronic bullous disease of childhood.[2] The term linear IgA dermatosis in adults was also coined in 1979. The terms LAD, linear IgA dermatosis of childhood, chronic bullous disease of childhood, linear IgA disease and linear IgA dermatosis in adults denote the same condition.

The cutaneous manifestations of LAD are variable. Peripheral vesiculation on erythematous macules or plaques, known as a 'string of pearls', is a characteristic clinical sign but is not always encountered and not pathognomonic for LAD. Several target antigens are recognized by autoantibodies, the main one being BP180 (full length, NC16A region, LABD97, LAD-1). BP230 is occasionally recognized in conjunction with BP180 and individual patients with predominant or exclusive IgA reactivity against laminin-332, p200 antigen and type VII collagen have rarely been described. In line, ultrastructural localization of immune deposits may occur at the *lamina lucida*, the *lamina densa*, or within the *lamina lucida* and the *sublamina densa* region.[3]

The aim of this project is to present the main clinical features of LAD in children and in adults, to propose a diagnostic algorithm and provide management guidelines based primarily on experts' opinion because of the lack of large methodologically sound clinical studies.

METHODOLOGY OF GUIDELINE PREPARATION

These guidelines were initiated by the European Academy of Dermatology and Venereology (EADV) Task Force Autoimmune Bullous Diseases (AIBD), and the writing group was formed at the Task Force meeting during the 29th EADV Annual Congress 2020.

To achieve a broad consensus, a total of 29 experts from different countries, both European and non-European, including dermatologists, paediatric dermatologists and paediatricians were invited. All members of the guidelines committee agreed to develop consensus-based (S2k) guidelines, according to the recommendations of the Association of the Scientific Medical Societies in Germany (AWMF; https://www.verwaltung.awmf.org/en/clinical-practice-guidelines/awmf-guidance/cpg-development.html). Prior to the first Consensus Virtual Meeting, each of the invited authors elaborated a section of the present guidelines focusing on a selected topic, based on the relevant literature. The first draft was discussed and corrected by all members of the guidelines committee prior to a hybrid Consensus Meeting held during the 31st EADV Annual Congress 2022.

During the second Consensus Meeting, all topics and questions were addressed before voting. Then, members of the writing group voted on all recommendations with 'agree', 'not agree' or 'abstention'. Recommendations with <70% agreement were rephrased, and voting was repeated.

To standardize the grade (level) of recommendations throughout this document, the following expressions were used (Table 1). For better visualization, levels were also labelled with colour-coded arrows. The consensus level was visualized by representative pie charts as shown in Table 2.

EPIDEMIOLOGY

LAD is a rare blistering autoimmune disease with two peaks of incidence according to age: one in adults aged between 60 and 65, and one in childhood. It is regarded as the most frequent AIBD in children.[4] Moreover, several cases of neonatal LAD have been reported, most of them associated with severe upper airway involvement and some with additional eye lesions.[5]

The overall incidence of LAD ranges from 0.25 to 1.0/million/year.[6–10] The incidence appears to be higher in developing

TABLE 2 Levels of consensus in these guidelines.

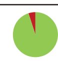
Level of consensus	Symbol
Strong consensus (agreement of >95% of participants)	
Consensus (agreement of >75-95% of participants)	
Agreement of the majority (agreement of 50-75% of participants)	

TABLE 1 Grades (levels) of recommendation in these guidelines.

Grade (level) of recommendation	Syntax	
Very strong recommendation (it is practically obligatory)	It is necessary	↑↑↑
Strong recommendation (some exceptions are acceptable)	It is recommended	↑↑
Less strong recommendation (one has to consider it but exceptions are not rare)	May be recommended	↑
Weak recommendation (it is allowed but it is not recommended as a rule)	May be considered	↑
Rejection (not recommended)	It is not recommended or it is contraindicated	↓

countries.[11–17] Its prevalence has been calculated to be 10.3/million inhabitants in Germany in 2014.[18] The prevalence in minors was shown to be higher (24.5/million minors).[19] Due to lack of larger studies, data about gender predominance are inconclusive. While a female predominance was observed in some reports,[4,19] other case series suggested that male patients are more frequently affected than females, at least in the paediatric and drug-induced variants.[20–23]

GENETICS

So far, there have been only few studies focused on the genetic background of patients affected by LAD. LAD is significantly associated with the expression of the human lymphocyte antigens (HLA) Cw7, B8 and DR3 and DQ2.[24] DR2 is present in most of the non-DR3 patients, while DR1, DR4 and C4 are less frequently expressed.[24] According to the age of onset, different HLA-genotypes are found.[24] Specifically, in childhood LAD, a significantly increased frequency of the HLA-Cw7, -B8, -DR3 and -DQ2 haplotype was described.[24] In contrast, in adult LAD, HLA-Cw7 was the only significantly increased HLA-antigen.[24] Expression of the haplotypes -B8, -DR3 and -DQ2 might favour early disease development.[24] In both adult and childhood LAD, the disease is associated with a TNF2 haplotype. In patients expressing the TNF2 haplotype, the duration of LAD appeared to be longer than in those expressing a TNF1 allele.[24] HLA-haplotypes in LAD patients differ according to the ethnic background.[14] Further epidemiological studies are needed to better substantiate these data.

PATHOPHYSIOLOGY

LAD is an immunologically heterogeneous condition. IgA autoantibodies from LAD sera bind to different proteins involved in promoting dermo-epidermal and/or epithelial-stromal cohesion. While the isotype-specific immunoregulation responsible for the characteristic IgA response in LAD remains to be elucidated, a significant subgroup of LAD patients also exhibits a concomitant IgG response to the same autoantigens.[25,26]

Immunoelectron microscopy studies in LAD have shown that immunoreactants exhibit different ultrastructural localizations. In most cases, IgA antibodies are bound to the uppermost part of the *lamina lucida* and to the basal surface of the hemidesmosomes. Less frequently, IgA deposits are found within the *lamina densa* and *sublamina densa* regions. Finally, in a few cases, a so-called 'mirror' image pattern is observed with immunoreactants deposited on each side of the *lamina densa*.[27,28] These variable patterns, which are also observed when sera are tested by indirect immunofluorescence microscopy (IIF) using salt-split normal human skin, reflect the presence of different antigenic targets in LAD.

Biochemically, most IgA autoantibodies from LAD sera characteristically bind to a 97-kDa protein and/or a 120-kDa protein, which are called LABD97 and LAD-1, respectively.[29,30] These two antigens represent proteolytic products of the extracellular domain of the BP antigen 180 (BP180, also called BPAG2 or type XVII collagen). The latter is a type II transmembrane hemidesmosomal protein with a large collagenous extracellular region.[31,32] The ectodomain of BP180 is proteolytically cleaved close to the transmembrane domain from the keratinocyte cell surface by distinct membrane-anchored metalloproteinases of the ADAM (a disintegrin and metalloproteinase) family.[33] LAD-1 lacks the N-terminal portion of the shed BP180 ectodomain, whereas LABD97 is produced by further cleavage of LAD-1 within the non-collagenous (NC) 4 domain of its C-terminal region.[30,34] Thus, LABD97 lacks parts of the N- and C-terminal portions of the BP180 ectodomain. Plasmin is also able to cleave the ectodomain of BP180 into the LABD97 antigen in an ADAM-independent manner during inflammation.[35] The exact N-terminus of LABD97 may thus vary according to its proteolytic processing.[34,36] In contrast to BP, in which IgG antibodies preferentially target full-length BP180 as well as the 120 kDa soluble extracellular domain with immunodominant antigenic determinants contained in a distinct portion of NC16A domain, IgA autoantibodies from LAD sera less frequently recognize full-length BP180 and the NC16A domain of BP180, but bind in up to 50% of cases to the soluble LAD-1 antigen.[25,26,37,38] Hence, processing of the BP180 ectodomain is necessary for the exposure of neo-epitopes specifically recognized by IgA autoantibodies and thus critically contributes to the pathogenesis of LAD.[39] The role of the physiologic shedding of the BP180 ectodomain remains unclear but might have an impact on keratinocyte adhesion, differentiation or migration.[33,40] In LAD sera, IgA reactivity with full-length BP180 or the BP180 NC16A domain is observed in 30%–40% of cases[35,38,41] while binding to the BP antigen 230 (BP230 or BPAG1-epithelial isoform), an intracellular hemidesmosomal protein, is observed in only 10%–20% of cases.[38,41]

In a small subset of LAD sera, IgA autoantibodies have been shown to specifically bind to type VII collagen, the constituent of anchoring fibrils. The latter reactivity most likely accounts for the *sublamina densa* type of LAD[42,43] and is now called IgA epidermolysis bullosa acquisita (EBA). These patients are presently classified as having EBA due to their reactivity against type VII collagen and are excluded from the group of LADs.

Finally, there are few reports which have shown that LAD sera also rarely react with laminin-332 or laminin-γ 1.[44–47] The presence of reactivities with different autoantigens as found in some LAD sera most likely reflects an intermolecular epitope spreading phenomenon.

The direct pathogenic role of IgA anti-LAD-1 and anti-LABD97 autoantibodies has not been yet unequivocally demonstrated. IgA antibodies bound to the dermo-epidermal junction (DEJ) are potentially able to activate the alternative complement pathway, triggering thereby an inflammatory response. IgA can further directly bind to specific Fc alpha receptors present on myeloid cells such as neutrophils, eosinophils and monocytes, and activates these cells.[48,49] In lesional skin obtained from LAD patients, the inflammatory cell infiltrate is predominantly composed of neutrophils, eosinophils and T cells with a TH2-dominated cytokine pattern. The tissue damage most likely results from proteases, including plasmin and neutrophil elastases as well as reactive oxygen species derived from neutrophils, eosinophils and mast cells.[49,50]

In a mouse model, passive transfer of an IgA monoclonal antibody to LABD97 into severe combined immunodeficient mice with human skin transplant resulted in the binding of IgA to the human DEJ, which in turn led to inflammation and subepidermal split formation.[51] This observation provides support to the idea that IgA antibodies directly contribute to tissue damage.

IgA can interact with the Fc receptor FcαRI (CD89) on immune cells, such as neutrophils.[52] A novel LAD model in genetically modified mice that express human FcαRI and generate human IgA demonstrated that repeated injections of human anti-BP180 IgA resulted in neutrophil activation and extravasation from blood vessels into skin tissue, massive neutrophil accumulation, severe tissue damage and subepidermal blister formation.[52] Administration of anti-FcαRI monoclonal antibodies prevented the disease and was able to resolve the existing chronic inflammation and tissue damage.[52]

DRUG ASSOCIATION

Several drugs appear to have the ability of triggering LAD,[49,53–55] among which vancomycin is the most frequent.[55] Drug-induced LAD (DILAD) has been described in adults and, less frequently, in children. In approximately one third of patients, the onset of LAD appears to be induced by exposure to other drugs than vancomycin[56,57] (Table 3).

Different pathogenic mechanisms have been discussed and hypothesized in the development of DILAD. A recent study focusing on vancomycin-induced LAD cases has provided evidence that LAD sera either acquire reactivity or show an increased reactivity with type VII collagen in the presence of vancomycin.[55] Vancomycin appears thus to enhance IgA reactivity with type VII collagen rather than modifying the autoantigen. These findings give new insights into mechanisms by which drugs may specifically contribute to the occurrence of DILAD and, in general, induce autoimmunity. However, as mentioned above, DILAD with reactivity against type VII collagen is excluded from the group of LAD and should be classified as drug-induced IgA EBA.

Most cases of vancomycin-induced LAD have been consistently associated with its intravenous administration.[58] Vancomycin-impregnated devices used in arthroplasty (e.g., vancomycin-impregnated cement spacer or bone cement) have also been reported to trigger LAD.[59,60] The development of vancomycin-induced LAD does not appear to be dose-dependent.[61]

TABLE 3 Non-exhaustive list of drugs reported in DILAD.[49,54,58–64]

Antibiotics: vancomycin, trimethoprim-sulfamethoxazole, penicillins, cephalosporins
Non-steroidal anti-inflammatory drugs: diclofenac, piroxicam, naproxen, acetaminophen
Antihypertensives: captopril, candesartan, verapamil, amlodipine
Antiarrhythmic: amiodarone
Diuretics: furosemide
Statins: atorvastatin
Anticonvulsants: phenytoin, vigabatrin
Vaccines: influenza, COVID-19

CLINICAL FEATURES

Neonates and children

Childhood LAD most frequently occurs between the age of 2–6 years. It may appear after viral infections or routine childhood vaccinations.[62] Lesions begin as vesicles on an erythematous base and rapidly fill with fluid to expand into tense bullae. Often, there is an annular pattern with an expanding edge of small bullae joining together (Figure 1), with an arrangement described as 'a string of pearls'.[63–66] The periorificial areas, the face, neck and groin/perianal are commonly involved sites in children. The scalp, palms and soles may be also involved.[62]

The rare cases of neonatal LAD favour the mucous membranes, and it is a much more severe disease than all other neonatal AIBDs.[65] In neonates, the lesions develop either at birth or within the first 2–4 weeks thereafter.[65,67–72] The oral and respiratory mucosae are often involved. Ocular involvement

FIGURE 1 Typical annular vesicles clustered on the thighs of a young child (Image courtesy of Antonio Torello, Spain).

may present as sterile conjunctivitis. Fever may occur.[69] Males are predominantly affected by far (19:1 over females).[62]

Adults

LAD in adults typically presents with polymorphic annular and polycyclic erythematous urticarial papules and plaques and widespread vesicles and blisters with rosette configuration ('string of pearls' sign). The eruptions often favour the trunk, extremities, palms, soles and spares the head and neck. Additional mucosal involvement occurs in a minority of patients although cutaneous lesions are always predominating.

Drug-induced LAD

Although the overall clinical presentation may not substantially differ between the idiopathic form and DILAD in a number of patients,[73,74] there are some distinct features in LAD which may be suggestive for a drug trigger (Table 4).

The eruption in DILAD typically appear within 9 days (median time) after exposure to the incriminated drug, even if the drug has been in the meantime discontinued. Nonetheless, DILAD has also occurred anecdotally within a few hours or 1 day after drug administration, such as with vancomycin.

DIFFERENTIAL DIAGNOSIS OF LAD

LAD needs to be differentiated from other dermatoses characterized by pruritus, blisters and erosions particularly where there is deposition of linear IgA at the DEJ. The conditions described below are important differentials (Table 5).

The differentiation of LAD from bullous impetigo, certain variants of prurigo and nummular eczema, lichen planus, as well as atypical forms of erythema multiforme, Stevens–Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) may sometimes pose a challenge, particularly in case of DILAD. The latter may mimic severe drug eruptions.

DIF and IIF on salt-split skin and, when required, ELISA and immunoblot are necessary to diagnose and differentiate LAD from other AIBDs (Table 5).

DIAGNOSIS

Histology

The histological features of LAD most commonly comprise subepidermal splitting with a neutrophil-predominant infiltrate.[20,75] In some cases, fibrin deposition and leukocytoclasia in the dermal papillary tips (a feature also present in DH) can also be found.[75] The dermal infiltrate consists predominantly of neutrophils but in up to 60% of cases may also contain some eosinophils.[3]

TABLE 4 Clinical features suggestive of a drug origin of LAD.

- Positive Nikolsky sign
- Presence of large erosions
- SJS/TEN-like clinical appearance
- Flaccid bullae with skin sloughing
- Palmo-plantar involvement with bullous lesions, haemorrhagic lesions mimicking vasculitis and/or targetoid, erythema multiforme-like lesions
- Morbilliform eruption
- Oral or conjunctival mucosal involvement

TABLE 5 Differential diagnoses for LAD.

Main differential diagnoses for LAD: autoimmune bullous diseases
Bullous pemphigoid (mainly IgG reactivity)
Epidermolysis bullosa acquisita (reactivity against type VII collagen)
Mucous membrane pemphigoid (predominant mucosal involvement)
Dermatitis herpetiformis
Pemphigus group: pemphigus vulgaris, pemphigus foliaceus, pemphigus herpetiformis (IgG reactivity against desmosomal antigens)
Intercellular IgA epidermal dermatoses (IgA pemphigus)
Paraneoplastic pemphigus/ paraneoplastic autoimmune multiorgan syndrome (PNP/PAMS)
Subcorneal pustulosis (Sneddon-Wilkinson disease)
Main differential diagnoses for LAD: other dermatoses
Bullous impetigo (detection of Staphylococcus aureus)
Bullous tinea corporis (positive mycological findings)
Varicella/zoster infection (positive varicella/zoster PCR)
Sexual abuse in case of genital involvement (negative serology)
Nummular eczema / chronic prurigo (negative serology)
Erosive lichen planus (negative serology)
Erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (negative serology)

Direct immunofluorescence microscopy

Linear deposits of IgA along the DEJ are the characteristic finding as detected by direct immunofluorescence microscopy (DIF) of perilesional skin. Approximately 20% of patients may also have granular IgA deposition at the DEJ.[76] Furthermore, concomitant linear deposits of C3 and, less frequently, of IgG are occasionally also found.[75] The labelling intensity of IgG is weaker than that of IgA. When both IgG and IgA deposits are found with similar staining intensity, the distinction of LAD from BP and other subepidermal AIBD such as EBA becomes challenging.[66,77–79] Although some authors have proposed to describe these cases as having linear IgA/IgG disease,[77] the latter concept remains questionable. Along this line, it may be hypothesized that LAD and BP represent a spectrum of an anti-BP180 pemphigoid disorder. This view is supported by the observation that the serum anti-DEJ autoantibody isotype is related to the patients' age, that is IgA anti-DEJ reactivity is associated with younger age and IgG anti-DEJ reactivity preferentially seen in older patients.[11]

The serration pattern analysis by DIF allows to distinguish an n- or u-serrated linear pattern of IgA and/or IgG deposits along the DEJ.[80] An n-serrated pattern is typically observed in skin biopsy specimens obtained from patients with the most common *lamina lucida* subtype of LAD as well as in BP and most cases of mucous membrane pemphigoid (MMP). In contrast, a u-serrated pattern is typical for the rare *sublamina densa* type of LAD (now classified as IgA EBA) and some cases of MMP.

Indirect immunofluorescence microscopy

Circulating IgA autoantibodies against the DEJ are detectable in up to 70% of cases by IIF using either monkey oesophagus or, preferably, salt-split normal human skin. Use of the latter allows to increase sensitivity.[20,38,41,81] LAD serum autoantibodies usually bind to the epidermal side of salt-split skin. Both IgA and IgG labelling can also be observed in LAD as well as in BP and MMP. If available, the BIOCHIP mosaic-based IIF assay represents a useful diagnostic tool, particularly for screening.[80,82] However, its use has not been validated in a larger LAD cohort yet.

Western blot/immunoblotting

Immunoblotting studies using epidermal extract or concentrated conditioned supernatant of cultured keratinocytes typically reveal IgA reactivity with LAD-1, the proteolytically cleaved extracellular domain of BP180, and/or LABD97, a smaller derivative of the latter. LAD-1 and LABD97 represent the two major target antigens of LAD.[29,30,38,83,84] Some LAD sera also recognize full-length BP180, BP180 NC16A or BP230.[85–87] LAD sera also rarely react with laminin-332, p200 antigen and type VII collagen.[88–90]

Immunoelectron microscopy

Direct immunoelectron microscopy demonstrates IgA immune deposits at different ultrastructural levels: (i) hemidesmosomes and upper *lamina lucida*, (ii) *lamina densa*, or (iii) *lamina lucida* and under *lamina densa* ('mirror' image).[28]

Diagnostic criteria

It is recommended to make the diagnosis of LAD if criteria 1 and 2 are fulfilled:

1. Clinical manifestations compatible with LAD. Mucous membrane involvement must not be predominant over skin involvement. ↑↑↑
2. Positive DIF showing solely linear deposits of IgA along the DEJ, or of both IgA and IgG. In the latter case, fluorescence intensity of the IgA deposits must be stronger than that of IgG. ↑↑↑

Diagnosis when DIF is negative or not possible

In case DIF (criterion 2) is negative, it is necessary to repeat the biopsy for DIF. If DIF is repeatedly negative or not possible to be performed on site, it is recommended to make the diagnosis if at least one of the following criteria is fulfilled:

- Clinical manifestations compatible with LAD (non-predominant mucous membrane involvement) and positive IIF using salt-split normal human skin demonstrating IgA binding to the epidermal side or a combined epidermal-dermal staining ↑↑↑
- Clinical manifestations compatible with LAD (non-predominant mucous membrane involvement) and in case of negative DIF and IIF on salt-split skin:
    - positive western blot detection of IgA autoantibodies against LAD-1, LABD97, BP180, BP230, laminin 332 and/or the p200 antigen ↑↑↑
    - positive modified ELISA kit based on secondary anti-human IgA antibodies against LAD-1, LABD97, BP180, BP230, laminin 332 and/or the p200 antigen ↑↑↑

Algorithm for the diagnosis of LAD

The recommended algorithm for the diagnosis of LAD is shown in Figure 2.

When repeated DIF and IIF on salt-split skin are negative, western blotting should be performed in case of high clinical suspicion (exclusion of differential diagnosis).

If LAD patients have IgA autoantibodies against type VII collagen, it is recommended to classify them as IgA EBA ↑↑↑ .

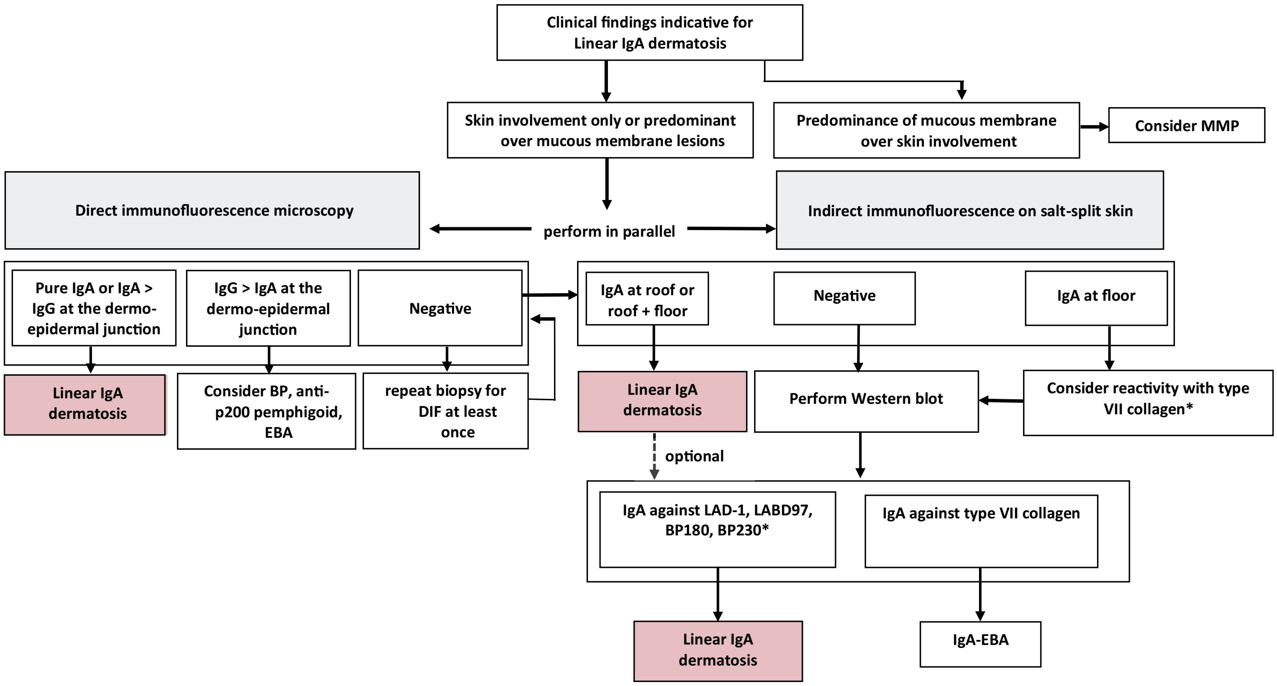


FIGURE 2 Diagnostic algorithm for linear IgA dermatosis. ↑↑↑ BP, bullous pemphigoid; DIF, direct immunofluorescence; EBA, epidermolysis bullosa acquisita; MMP, mucous membrane pemphigoid. *In isolated cases, IgA reactivity against laminin 332 and the p200 antigen has been described.

TABLE 6 Assessment for comorbidities and potentially causative trigger factors.

• A drug trigger is necessary to be considered in each case of LAD, especially in adult patients with comorbidities	↑↑↑
• Ulcerative colitis may precede or coincide with the development of LAD skin lesions. Work up is necessary	↑↑↑
• Investigation for potentially culprit drugs is recommended and if there is a suspected induction it is necessary that the drug is withdrawn	↑↑↑
• Work up for an underlying infection, e.g., *Helicobacter pylori* gastritis, may be considered	↑
• In adult patients with LAD, it is necessary to perform a standard age-appropriate malignancy screening for an underlying cancer (lymphoproliferative diseases, visceral neoplasms), especially if medical history is suggestive (e.g., unintended weight loss)	↑↑↑
• Due to possible LAD complications or associations with other autoimmune or malignant diseases, some additional consultations with rheumatologist, gastroenterologist, hematologist, ophthalmologist, etc. may be considered at diagnosis and during follow-up	↑

WORK UP BEFORE INITIATION OF THERAPY

Assessment for comorbidity and potentially causative trigger factors

LAD usually develops spontaneously, but it may be associated with certain medications (see above) or underlying diseases (Table 6):

Ulcerative colitis has been described in 7% of British LAD patients,[81,91] and up to now more than 30 cases with concurrent occurrence of both diseases have been published.[41,92] Usually, the diagnosis of ulcerative colitis precedes the development of skin lesions or the diagnosis is made simultaneously. Complete remission of LAD after colectomy has been described.[38,82,93,94]

Underlying infection, for example, *Helicobacter pylori* gastritis, has been described to precede the onset of LAD.[30,95]

Underlying malignancy is rarely associated with LAD. There are anecdotal reports of *lymphoproliferative diseases* (Non-Hodgkin lymphoma, leukaemia) as well as visceral neoplasms (e.g., bladder, thyroid, renal and oesophageal cancer) in association with LAD.[83,84,96,97]

DILAD

Histopathology of skin biopsy of DILAD shows subepidermal splitting with typically a predominantly neutrophilic dermal infiltrate that may be intermingled by eosinophils. DIF of perilesional skin demonstrates only IgA deposits and no concomitant

IgG and/or C3 at the DEJ. IIF using monkey oesophagus or normal salt-split human skin is often negative.

If a medication is suspected to be responsible for LAD drug causality assessment has to be performed. A Naranjo probability score consisting of 10 questions could be used and causality is probable if the score is >4.[21] Provocation tests are usually not performed; in a few cases, drug rechallenge was associated with a relapse of the eruption.[21] A rapid drug withdrawal of the putative trigger is important. DILAD (including drug-induced IgA EBA) is thought to have a favourable course with remission in at least 75% of cases when the culprit drug is omitted. A subset of the latter had not even received any specific treatment.[21] However, DILAD can persist for several weeks or even show relapses despite drug withdrawal.

TREATMENT

Data on the effectiveness of treatments in LAD are based on case series, retrospective single-centre studies, anecdotal case reports or expert opinion. In the majority of cases, a systemic treatment is needed (Table 7).

There is a clinical consensus that dapsone is the first choice for LAD treatment, being repeatedly reported to be the most effective drug in managing this condition with excellent initial responses and long-term remissions. Although dapsone is sufficient as monotherapy in most cases, it can be combined with other drugs for better results in recalcitrant cases. Those include sulfonamides (sulfapyridine, sulfasalazine and sulfamethoxypyridazine), which are generally considered alternatives to dapsone and may be used alone or in association with it and systemic or topical corticosteroids, the use of which may be required especially in situations where side effects limit the recommended daily dose of dapsone.[98] Combination with immunosuppressants, such as azathioprine, mycophenolate mofetil,[99,100] ciclosporine, cyclophosphamide and topical tacrolimus may be necessary in some cases.

There are cases which have been managed avoiding the use of dapsone, for example by applying pulsed corticosteroids,[101] colchicine,[102] antibiotics, such as erythromycin, the combination of tetracycline and niacinamide (nicotinamide),[103] trimethoprim-sulfamethoxazole and oxacillin,[104] but also intravenous immunoglobulin and immunoadsorption.[105,106] A few case reports described the use of rituximab.[107]

Systemic therapy is required until patients achieve complete clinical remission, after which maintenance of the drug dosage should be adjusted according to the clinical evaluation of (muco)-cutaneous lesions. In case of recurrence, systemic therapy should be restarted and continued over weeks or months after the complete disappearance of all lesions.[105] To guide cessation of dapsone therapy, repeating DIF microscopy may be considered and dapsone discontinued in case of negative DIF.[108]

TABLE 7 Treatment options reported in the literature for LAD.

	Pharmacological treatments	
First line	Dapsone +/- topical corticosteroids	↑↑↑
Second line	Sulfapyridine	↑↑↑
	Sulfasalazine	↑↑↑
	Systemic corticosteroids*	↑↑↑
	Erythromycin	↑
	Colchicine	↑↑
	Dicloxacillin	↑↑
	Flucoxacillin	↑↑
	Trimethoprim-sulfamethoxazole	↑↑
	Tetracycline and niacinamide	↑↑
Third line	Sulfamethoxypyridazine*	↑↑↑
	Mycophenolates*	↑↑↑
	Azathioprine*	↑↑↑
	IV immunoglobulins	↑↑↑
	Ciclosporin	↑↑↑
	Methotrexate	↑↑↑
	Infliximab	↑↑
	Etanercept	↑↑
	Rituximab	↑↑↑
	Omalizumab	↑
	Cyclophosphamide**	↑

*As monotherapy or in association with dapsone.

**Cyclophosphamide may be considered as a last resource, only in case of contraindication or failure of previously reported treatment approaches in adults, while it is contraindicated in children.

General recommendations

DILAD may be identified both with Naranjo score and a close temporal relationship between drug introduction and rash development or rash disappearance upon drug withdrawal.

Topical treatments in association with systemic therapy should be carefully explained to the patient. Patients should be aware of the importance of monitoring emergence of new bullae and erosions, even by counting them (Table 8). It should be explained how to manage them in the earlier steps: that is begin by gently applying a desiccant solution to the exudative areas, followed by using bath products that

TABLE 8 General recommendations and patient support groups.

• It is necessary to inform the patient and/or parents about the chronicity of the disease and educate them to promptly recognize new lesions, emphasising that relapses may occur in different sites from the ones initially involved	↑↑↑
• It is recommended to inform the patient and/or parents about patient support groups. : IPPF (International pemphigus and pemphigoid foundation, USA) ANPPI (Italian National Association Pemphigus-Pemphigoid) APPF (Association Pemphigus-Pemphigoïde France) UNIAMO (Rare Diseases Italian Federation onlus) Australasian Blistering Diseases Foundation PEMfriends, Pemphigus and Pemphigoid patient support group (UK) Pemphigus and Pemphigoid- Selbsthilfegruppe (https://pemphigus-pemphigoid-selbsthilfe.de/), Germany	↑↑

TABLE 9 Dapsone is the first-line treatment for LAD.

• Dapsone is recommended as first-line treatment for LAD in all patients with normal G6PD activity.*	↑↑↑
• It is necessary to determine G6PD activity before initiation of dapsone.	↑↑↑

*Unless allergies against dapsone or sulfones are known.

TABLE 10 Optimal dose of dapsone.

• It is recommended to use a starting dose of dapsone of 25-50 mg/day in adults, 0.5-1 mg/kg in children. If adequate preparations are not available for children, then a drug compounding is recommended.	↑↑↑
• It is recommended to reach a daily dose of dapsone of 0.5-2 mg/kg in adults.	↑↑
• Treatment discontinuation may be considered when negative DIF is obtained from a previously positive lesion site.	↑

contain antiseptics and/or wheat starch. If dealing with widespread erosive lesions, consider using non-adhesive dressings to cover them. This helps to minimize the risk of additional blistering and infection, reduces discomfort and promotes the healing process. For addressing erosive lesions, topical corticosteroids like betamethasone dipropionate can be employed. Oral mucosa lesions may be treated, if accessible, directly applying a combination of topical high potency corticosteroids and adhesive paste. Dental procedures should be avoided during acute phases of the disease.[108]

Patient support groups

Herein are reported some European support groups for patients affected by LAD (Table 8).

Dapsone

Dapsone (4,4-diaminodiphenyl sulfone) is an antibiotic and anti-inflammatory compound commonly used for the treatment of neutrophil-mediated dermatoses, including DH, as well as diseases characterized by neutrophil adherence to IgA.[109]

It is the treatment of choice for LAD (Table 9). When it leads to a partial response, other drugs may be used in combination with dapsone.[110,111]

After the appropriate confirmatory diagnosis of LAD oral dapsone could be administered at a starting dose of 50–100 mg/day, a dosage to be adapted to the therapeutic response and to be maintained until the disease is controlled.[108] Other authors recommend that it should be started at a lower dose (25 mg/day in adults) and then gradually increased according to the clinical condition, particularly by the emergence of new lesions, at weekly intervals to a dose of 100–200 mg/day.[105,112]

The majority of patients with cutaneous disease respond effectively to dapsone as a first-line therapy at dosages of 50–200 mg/day. This response is usually rapid and occurs within some days.[113] Adverse effects to dapsone usually manifest when a daily dose of 100 mg is reached with the need to reduce it to 50 mg/day.[98,109] Hence, it may be safer to start with a dose of 25 mg daily and then to gradually increase it according to the individual response in order to detect early possible idiosyncratic reactions and manifestations of intolerance. This may be particularly true for elderly patients who are anaemic, have ischaemic heart disease or suffer from a reduced lung capacity. However, in young adults without comorbidity an initial dose of 50 mg may be appropriate. Then, the dosage could be adjusted according to the actual weight, considering 0.5–2 mg/kg/day as the optimum dosage. In children, doses of up to 3 mg/kg/day may be recommended to achieve an optimal clinical effect (Table 10).

Dapsone exhibits good bioavailability, but serum levels can have a wide variation; therefore, measuring serum dapsone levels as a guide to therapy has little value. There is wide variability in the half-life of dapsone (10–50 h), but it is reported that the vast majority of patients are best managed on a single daily dose.[112]

The side effects of dapsone may be categorized as pharmacologic (dose-dependent) and allergic (idiosyncratic). Among dose-related side effects, the most common is haemolysis which typically results in a reduction of haemoglobin levels by 15–20 g/L. Therefore, it is advisable to maintain a baseline haemoglobin level within the normal range. Since dapsone is a strong oxidizer, it may produce severe haemolysis which is caused by the metabolite hydroxylamine in patients with glucose-6-phosphate-dehydrogenase (G6PD) deficiency. Therefore, patients should be screened for G6PD deficiency before starting dapsone therapy. Assessment of G6PD deficiency is possible by detection of enzymatic activity (by spectrophotometric testing, fluorescence testing or formazan-based spot testing) or by molecular analysis for mutations of the gene encoding G6PD.[114] Methaemoglobinaemia occurs in less than 15%; at high dose, it may become symptomatic with the development of cyanosis, weakness, headaches, dyspnoea and tachycardia. It is inevitable during dapsone treatment and may be considered a marker for regular drug intake. In adults, methaemoglobin levels of up to 7% can be tolerated unless clinical symptoms appear. To reduce haemolysis and methaemoglobinaemia and treat associated headaches, ascorbic acid (at least 500 mg a day) or vitamin E (400 mg 3 times a day) may be recommended additionally.

Other less frequent side effects include a sensory and motor neuropathy, toxic hepatitis and cholestatic jaundice, and hypoalbuminaemia or eosinophilic pneumonia.[112,115] Idiosyncratic side effects may present as psychiatric symptoms, infectious mononucleosis-like syndrome, exfoliative dermatitis, erythema multiforme, erythema nodosum and urticaria. Dapsone hypersensitivity syndrome is a rare idiosyncratic adverse reaction that manifests with the clinical triad of fever, rash and internal organ involvement, the last of which may be fatal. In a similar fashion, unpredictable agranulocytosis can occur.[116]

Patients on dapsone therapy should have a baseline complete blood count (CBC), liver function tests and a G6PD level. Hypo- or agranulocytosis may emerge within the first 3 months of treatment, possibly due to low activity of the N-acetyltransferase-2 enzyme.[117] Hence, blood cell count should be checked weekly for the first month, every 2 weeks for the next 2 months, and at least every 3 months thereafter.

TABLE 11 The following clinical and laboratory examinations before and during dapsone therapy are recommended.

Frequency	Recommended examinations	↑↑↑
Baseline	History and clinical review CBC Liver function panel Renal function panel Blood G6PD level (if not available, reduced starting dapsone dose is recommended)	
First month: weekly **Second and third month: every two weeks**	History and clinical review CBC including reticulocyte count MetHb if daily dose>150 mg	
First three months: every two weeks	CBC including reticulocyte count Liver function panel Renal function panel	
Every third month	History and clinical review including peripheral motor neurological examination CBC including reticulocyte count Liver function panel Renal function panel	

Abbreviations: CBC, complete blood counts; MetHb, methaemoglobin level.

A chemistry profile should be repeated every 6 months to monitor for possible hepatotoxicity, changes in renal function and hypoalbuminaemia (Table 11).[112] Dose-related side effects are more frequent in patients with G6PD deficiency, comorbidity reducing tissue oxygenation and in the elderly. Thus, in patients with comorbidity or abnormal laboratory values, more frequent follow-ups, dose reduction of dapsone or interruption of therapy may be recommended.[118]

Regarding its teratogenic risk dapsone is classified as B2 according to the *Australian Drug Evaluation Committee*, thus being a drug for which no sufficient data concerning assumption during pregnancy with respect to, for example, malformations, direct and indirect toxic effects on the foetus, and serious problems during labour have not been clearly reported yet. Therefore, although it is known that it can cross the placenta and it is secreted into breast milk, dapsone is generally regarded to be safe for both mother and foetus. Nevertheless, there is a theoretic risk of methaemoglobinaemia and mild haemolytic anaemia, leading to hypoxia.[119] Case reports of LAD analysing the use of dapsone during pregnancy document that there is a general clinical improvement, even after reducing or discontinuing it.

Main contraindications for dapsone include G6PD deficiency, allergy to sulfonamides, anaemia, neutropenia, significant cardiopulmonary disease, significant liver or renal function impairment, frequent and/or severe headaches, and peripheral motor or sensory neuropathy (Table 11).

Sulfonamides

Sulfonamides, including sulfapyridine, sulfasalazine and sulfamethoxypyridazine, are alternatives to dapsone and may be used alone or in combination with it. They are regarded to be less effective than dapsone and are less available; their use is rare in Europe.[105,118] The range of dose administration is wide, as it is reported to be of 15–60 mg/kg/day (3–6 g/day).[108] Doses in children are 100–200 mg/kg daily in three to six divided doses.[22,120] The three drugs have similar profiles concerning adverse effects (anaplastic anaemia, agranulocytosis, thrombocytopenia, haemolysis, leukopenia, hepatotoxicity, hypersensitivity pneumonitis, lupus-like syndrome, pancreatitis, nephrolithiasis, urticaria, erythema multiforme, SJS, allergic vasculitis, fever).

Corticosteroids

In mild forms of adult LAD, topical corticosteroids can be used alone without the need for systemic treatments. In more severe disease states, they can be combined with systemic treatment to limit therapy doses. Potent topical corticosteroids such as clobetasol propionate are generally preferred.[49,105,113]

Systemic corticosteroids may be a primary option when dapsone or sulfonamides cannot be used because of their significant potential side effects (for example, in G6PD deficiency, dapsone hypersensitivity, severe anaemia or organ failure).[101]

For patients who are refractory to dapsone therapy or those who are achieving only partial response, prednisolone may be tried in combination with dapsone at doses of 0.5 mg/kg daily (mild to moderate doses) to achieve optimal control.[22,110,113] Systemic corticosteroids may be an option for combination therapy in patients with mucous membrane involvement, typically refractory to dapsone monotherapy.[113] Moreover, systemic corticosteroid therapy, alone or sometimes in combination with immunosuppressants, may be necessary in severe disease in which there is no adequate response to dapsone.[105,108]

In LAD developing during pregnancy, systemic prednisolone may be the initial treatment before adding dapsone.[121]

Other treatments

Patients with LAD most often respond dramatically to dapsone or sulfapyridine alone. In patients who are intolerant to these medications or experiencing recalcitrant LAD, second-line therapeutic agents may be considered.

Colchicine has been reported to be an efficacious and well-tolerated treatment for numerous dermatologic diseases including LAD.[122] However, the data on treatment of LAD with colchicine are mostly limited to case reports or small case series. Some authors have achieved satisfactory results with 0.5 mg of colchicine twice daily in childhood LAD cases,[123–125] but experience in adult patients is scarce. There are some adult LAD case reports that colchicine treatment, administered at doses of 0.5 mg 1–3 times a day, effectively and safely suppresses symptoms for months without relapses, starting within 5–10 days.[102,126,127] Colchicine is generally well tolerated. Side effects are dose-dependent and include nausea, vomiting, abdominal pain and diarrhoea. Leukopenia and agranulocytosis are rare.

The combination of *tetracycline and niacinamide* (syn. nicotinamide) has been reported to be useful in the treatment of BP and other AIBD.[128–130] Tetracycline 500 mg t.i.d. and niacinamide 600 mg t.i.d. provided complete or almost complete remission within 2–3 weeks in some patients with LAD.[103,131,132] A combination of tetracycline and niacinamide seems to have a safety profile broader than that of dapsone or prednisone therapy.[129,130] Niacinamide alone has been used with success in very young patients in whom there is a relative contraindication for using tetracyclines.[133] Therefore, it may be considered as an alternative in cases of LAD that have contraindications for dapsone and prednisone, for children and for mild disease.

Trimethoprim-sulfamethoxazole and *topical tacrolimus* were reported to be helpful when used in conjunction with other immunosuppressants as second-line adjuvants.

Mycophenoles: They include mycophenolate mofetil and mycophenolic acid, administered orally at dosages of 2 and 1.44 g/day, respectively.[134,135] There are few case reports describing the use of mycophenoles in LAD treatment.[99,100,136] Some authors suggest raising daily dose by 1 capsule per week for better gastrointestinal tolerance. Adverse effects to be considered are the following: anaemia, leukopenia, blurred vision, abdominal pain, gastrointestinal haemorrhage, nausea, diarrhoea, dyspnoea, haematuria, hypertension, tachyarrhythmia, acne, hepatotoxicity and arthralgia.

Intravenous immunoglobulins (IVIG): In a case series, monthly cycles of IVIG were administered along with colchicine and prednisone 15 mg/day. There was a good response and prednisone could be tapered until discontinuation after 5 cycles of treatment. The recommended dose is 2 g/kg given over 3–5 days in monthly intervals.[137] Potentially severe side effects in older patients, especially the risk of acute renal failure, must be considered. Anaphylactic reactions can occur in individuals deficient in IgA, but this is extremely rare in LAD. Other potential adverse effects are headache, back pain, chills, flushing, fever, myalgia, nausea, thrombophlebitis, aseptic meningitis, hypertension and congestive heart failure.[106]

Azathioprine: It is started for the first week at 50 mg/day to detect idiosyncratic reactions [and in this case stop immediately, regardless of thiopurine methyltransferase (TPMT) results] and then increased to the desired dose considering 1–2.5 mg/kg/day and according to TPMT activity.[49,138] Before initiating azathioprine, TPMT functional tests or genotyping are recommended since polymorphisms may lead to reduced enzymatic activity and increased toxicity (leukopenia). Low TPMT activity warrants dose adjustments (30%–80% of the normal dose). If such tests are not available, then a starting dose of maximum 50 mg/day is recommended which can be gradually increased after a few weeks if there are no dangerous changes in the CBC. Patients with a homozygous *NUDT15* (415C>T) mutation carry a higher risk of azathioprine-induced myelosuppression.[93,94,139,140] Dose reduction to 20%–40% of the normal dose is necessary in patients treated with azathioprine and allopurinol, but it is recommended not to prescribe these two drugs together.

Ciclosporin: Its maintenance dosage is 2–5 mg/kg/day. Potential adverse effects include nephrotoxicity, high blood pressure and neurotoxicity.[49] It is contraindicated above the age of 60.

Cyclophosphamide: It is only for the treatment of refractory cases in adults. It could be used in adults at a dose of 500 mg as IV bolus or given orally at 2 mg/kg/day.[138] Potential adverse effects include leukopenia, nausea, headache, hair loss, haemorrhagic colitis, haemorrhagic cystitis, bladder fibrosis, interstitial pulmonary fibrosis, amenorrhoea and malignancy, particularly bladder cancer.[49]

Methotrexate: According to the experience of the authors, methotrexate may be effective in a dose between 15 and 20 mg/week. It is a relatively safe option in the elderly with normal renal function. In a case of LAD associated with ulcerative colitis long-term 22.5 mg/week methotrexate administration was reported as an effective treatment to control both LAD and gastrointestinal issues.[141]

Biologics

Biologics may be considered an alternative in difficult-to-treat cases of LAD, non-responding to conventional therapies and in the case of contraindications to standard therapies, either as add-on therapy or as monotherapy. They might be used when LAD is associated with concomitant and possibly trigger diseases for which biologics are validated therapies.[142] In the literature, there are no reports of rituximab, etanercept or infliximab to treat children with LAD.

Infliximab: Although infliximab has been reported to induce LAD, probably as a paradoxical reaction, there is one report on infliximab having a marked effect on LAD in a patient with ulcerative colitis.[142] This might be due to infliximab directly antagonizing the increased levels of TNF-α present in LAD, as reported by Caproni et al.[50]

Etanercept: A case of an extensive DILAD mimicking TEN was reported to having improved and rapidly resolved after withdrawal of the offending drug and etanercept treatment.[143]

Rituximab: Three patients with refractory LAD were effectively treated by rituximab, whereas one patient was unresponsive to this biologic.[144,145]

Omalizumab: Omalizumab was effective in one case report of refractory LAD with relapse after cessation of this biologic and resolution upon reintroduction of omalizumab.[146]

Treatment of DILAD

Discontinuation of the offending medication may produce remission of DILAD. Typically, cessation of new lesion formation is observed 1–3 days after drug withdrawal and old lesions resolve within 2–7 weeks. In serious and persistent cases, additional therapy with dapsone, systemic corticosteroids (prednisone or prednisolone) 0.5 mg/kg to 1 mg/kg/day and/or topical glucocorticoids, colchicine or IVIG may be required to stop progression of the disease.[147]

Treatment strategies

First-line treatment of LAD is dapsone. In case of absence of control despite an adequate dose of dapsone or if it is contraindicated, a second-line drug is given and a third-line drug may be necessary in refractory LAD. Upon disease control, the dosage of dapsone is decreased until the minimum dose to avoid relapse is reached.

PROGNOSIS

Children

Childhood LAD is rare in Caucasian populations but more common in Asians and Africans, most likely because of the linkage with distinct HLA genes conferring susceptibility. Since African and many Asian populations have a high percentage of minors, the relative frequency of LAD is higher in these countries compared to Western communities. The disease is usually sudden in onset and worse during the first ‘attack’. Thereafter, it may become chronic and relapse.

Prognosis of LAD in children is generally favourable. It typically persists for months to several years prior to resolution (3–5 years). LAD resolves in most children prior to puberty. Related data are mostly based on small case series or single case reports. For example, the mean initial treatment time to achieve remission for a cohort of children with LAD in Denmark was 3.2 years (range 2–6 years),[22] while a series from Tunisia demonstrated a duration of 15 months (range 3 months–4 years) in 60% of patients (16/25).[148] In the same cohort, 30% of patients (8/25) had persistent disease after 18 months of treatment (range 12–24 months).[148] A series of 16 paediatric LAD patients from Kuwait showed all to be in remission and off treatment on follow-up, though this ranged widely from 2.5 to 156 months.[23] Complete remission off therapy was also seen in the majority (60%) of a small cohort of five paediatric LAD patients from Singapore at follow-up (range 2–51 months).[149] In the largest case series of 38 Italian LAD patients (27 adults, 11 children), possible differences in prognosis between adults and children were compared.[20] Relapses were rarely observed in either adults or children (4 adults, 1 child), with no statistically significant differences between adults and children.[20] None of the patients with relapsed disease were taking medication for their LAD at the moment of relapse.[20]

Neonatal LAD has been associated with severe mucosal involvement and respiratory failure.[67,72,150] Neonatal LAD was first reported by Hruza et al. in 1993.[67] Recently, a case of neonatal LAD has been shown to be due to passive transfer of pathogenic IgA from the asymptomatic mother via breast milk.[151] Breastfeeding interruption led to disease remission in the newborn and may be considered in neonates with suspected LAD.[151]

Even though LAD is generally regarded to resolve spontaneously within months to years, usually by puberty, persistence beyond puberty has been described. Some cases that have been in remission for many years may relapse after respiratory or other infections.[152] Permanent sequelae, including blindness and dysphagia, have been rarely described.[63]

Adults

LAD in adults has the reputation of being a rare but benign disease. Data on the long-term outcomes and prognosis of idiopathic LAD in adults are contradictory compared to its favourable evolution in childhood. Difficulty in the proper evaluation of its natural course in adults is explained with its rarity, controversial definition and lack of long-term follow-up.

Analysis of isolated clinical cases and small case series reported favourable outcome for most patients with clinical remission occurring after a mean of 5.6 years (range between 10 months –11 years).[153] Similarly, a retrospective Scandinavian LAD series found that the duration of the disease was long, and most adult cases could be effectively controlled with a mean duration of treatment of 4.1 years (range 1 month – 22 years, median 2 years).[22] No statistically significant difference was described in the treatment response between childhood and adult types of the disease, as well as between the IgA versus IgA/G types, or epidermal versus dermal types in larger cohorts of LAD patients from Japan and Italy.[20,154]

Other reports detected less frequent remissions in adult LAD, persistent course and a mean duration of disease of 7 years (range 2–40 years).[4] Difficulty in determining the duration of treatment was related to the fact that most cases relapsed during tapering of the medication and required a new dose increase.[98]

In an attempt to identify clinical and immunological factors predictive of complete remission, the analysis of 72 idiopathic LAD cases found that one third of the patients achieved sustained complete remission while two-thirds had chronic or relapsing disease. Major risk factors for persistent disease were age <70 years and presence of mucous membrane involvement (Table 12). On the contrary, age >70 years and absence of mucosal lesions were significantly associated with occurrence of complete remission.[41] No prognostic immunological factors were identified by immunofluorescence, immunoblotting or immunoelectron microscopy. Younger age and mucosal involvement may be suggestive for both treating physicians and patients of a significantly higher risk of a chronic evolution and prolonged treatment.[155] Thus, the patient's phenotype is relevant for choosing the therapeutic strategy. Other reports do not detect correlation between clinical severity and disease chronicity.[105]

DILAD in adults is usually reported to have favourable outcome with spontaneous regression of the lesions within days or weeks after withdrawal of therapy and reappearance of the eruption on reintroduction of the culprit drug.[153,156] A worse prognosis can be expected in older patients or in those with severe comorbidity, but not as a direct result of the DILAD.[157] Severe course and poor prognosis were also observed in 20% of the drug-induced cases, especially those related to vancomycin and clinically mimicking toxic epidermal necrolysis.[21]

Like with many autoimmune diseases, vaccination against SARS-CoV-2 during the COVID-19 pandemic has led to reports on vaccine-induced LAD.[158,159]

TABLE 12 Prognostic factors predictive for LAD chronicity in adults.

• Age < 70 years		↑
• Presence of mucous membrane involvement		↑

TABLE 13 Future perspective and gaps in knowledge.

• Demonstration of effectiveness of antibiotics in juvenile LAD	
• Sequence of the drugs in case of inefficacy or incomplete efficacy of dapsone	
• Choice of a specific treatment depending on the clinical/ immunological type of LAD	

In conclusion, LAD in adults has a longer and more persistent course as compared to the childhood type and prognosis depends on the patients' phenotype.

FUTURE PERSPECTIVE AND GAPS IN KNOWLEDGE

Several gaps of knowledge exist and need further investigations (Table 13).

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CONFLICT OF INTEREST STATEMENT

Conflict of interest related to these guidelines is given in Table S1.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

ETHICS STATEMENT

The patients in this manuscript have given written informed consent to publication of their images.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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