

PRACTICAL DERMATOLOGY

Practical Management of the Most Common Autoimmune Bullous Diseases

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Abstract. Autoimmune bullous diseases are relatively uncommon and their treatment—although generally similar—may vary depending on the dermatologist. Within this group of diseases, the most common are pemphigus vulgaris and pemphigus foliaceus, bullous and mucosal pemphigoid, linear immunoglobulin A disease, and dermatitis herpetiformis. In recent years, the therapeutic arsenal has been extended by new drugs, some of which have changed the prognosis of these diseases. This article describes current management protocols for these processes as indicated in the literature and derived from the experience of specialized clinics for bullous diseases. We also present the findings from an Internet survey on therapeutic approaches in pemphigus vulgaris answered by more than 40 dermatologists who work primarily in Spanish hospital clinics.

Key words: treatment, pemphigus, pemphigoid, dermatitis herpetiformis, linear immunoglobulin A.

MANEJO PRÁCTICO DE LAS ENFERMEDADES AMPOLLOSAS AUTOINMUNES MÁS FRECUENTES

Resumen. Las enfermedades ampollas autoinmunes constituyen un grupo de entidades relativamente infrecuentes cuyo tratamiento, aunque semejante, varía en función de las escuelas dermatológicas. Dentro de este grupo las más frecuentes son el pénfigo vulgar y foliáceo, el penfigoide ampolloso y de mucosas, la enfermedad IgA lineal y la dermatitis herpetiforme.

En los últimos años se han incluido en el arsenal terapéutico fármacos que han cambiado en ocasiones el pronóstico de las mismas.

Recogemos en este artículo los protocolos de actuación actuales en estos procesos basados en la literatura y en la experiencia de consultas monográficas de enfermedades ampollas. Así mismo, hemos recogido los datos de una encuesta vía internet sobre los métodos terapéuticos en pénfigo vulgar de más de 40 dermatólogos con experiencia habitualmente hospitalaria en España.

Palabras clave: tratamiento, pénfigo, penfigoide, dermatitis herpetiforme, IgA lineal

Introduction

In recent years, our understanding of bullous autoimmune diseases and their management has progressed significantly. This is partly thanks to the appearance of new entities based on determination of antigens, to the increased sensitivity and specificity associated with serologic diagnosis of some of these diseases (enzyme-linked immunosorbent assay [ELISA] for desmogleins in pemphigus vulgaris and pemphigus foliaceus, ELISA for BP180 in pemphigoid,

etc), and to advances in the understanding of the pathogenesis of the disease, as well as to the development of new therapies involving antibodies (rituximab) and intravenous immunoglobulin, which have been the subject of numerous review articles on these diseases.

In Spain we often base our approach to the treatment of these diseases on results obtained in British, German, or North American patients. Here, however, we have sought to compile data and experience from a group of Spanish dermatologists with an interest in this area. The aim of this review is not to be dogmatic, since there is no general or even regional consensus regarding the management of many of these diseases. Rather it is our hope to provide a practical review for use in day-to-day hospital-based practice through a combination of published findings and accumulated

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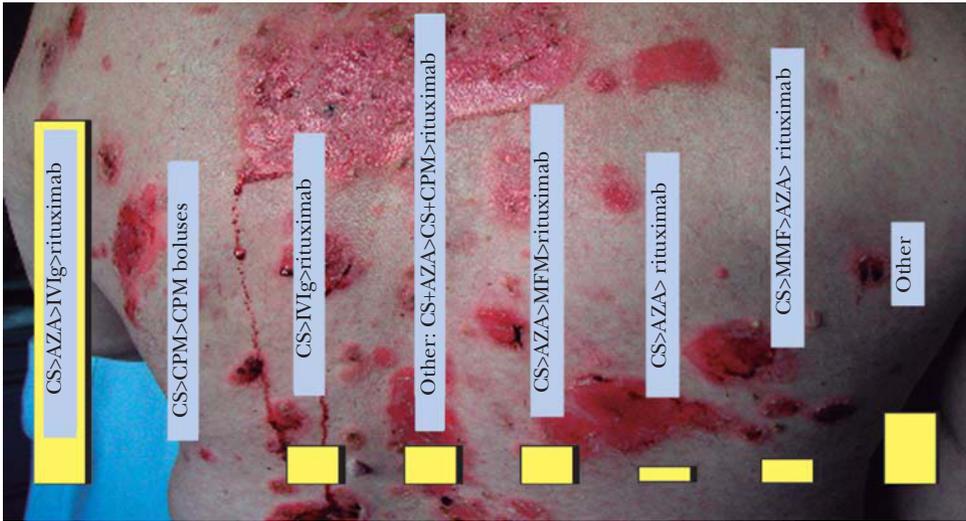


Figure 1. Treatment scale in pemphigus vulgaris. AZA indicates azathioprine; CS, corticosteroids; CPM, cyclophosphamide; IVIg, intravenous immunoglobulin; MMF, mycophenolate mofetil.

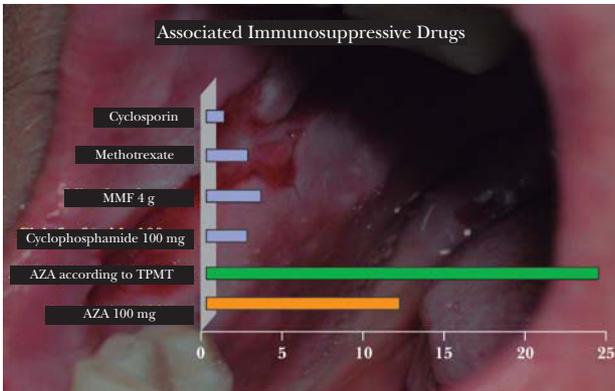


Figure 2. Which is the preferred steroid sparer? AZA indicates azathioprine; MMF, mycophenolate mofetil; TPMT, thiopurine methyltransferase

Treatment Options

Corticosteroids

Corticosteroids have anti-inflammatory and immunosuppressive effects and their pharmacology is understood. It is important to monitor their various side effects, both chronic and acute, which include adrenal insufficiency, electrolyte imbalances, hypertension, hyperglycemia, myopathy, immunosuppression, psychosis, cataracts, glaucoma, osteonecrosis and osteoporosis, infections, and gastrointestinal symptoms.^{1,2} Osteoporosis is monitored by yearly bone densitometry and controlled by administration of calcium, vitamin D, and bisphosphonates (weekly tablets are available).

Azathioprine

Azathioprine (Imurel capsules, 50 mg) is an inhibitor of purine synthesis and is the “steroid-sparing” immunosuppressive drug favored by most Spanish dermatologists consulted (Figure 2). It has been used for the treatment of pemphigus vulgaris since 1969 with a reported efficacy of 55%. Given that in Spain analysis of its metabolic enzyme (thiopurine methyltransferase) is available, we request this information in order to adjust the dose, since the initial 50 mg every 12 hours is usually too low and doses of up to 2.5 mg/kg/d can sometimes be tolerated. In order to prescribe such doses, we must confirm that there is no enzyme deficiency, since 0.5% of the Spanish population lacks this enzyme completely and 11.9% display partial deficiencies. The patients may suffer serious side effects (cholestatic hepatitis, severe myelosuppression, pancreatitis, and gastric toxicity). A therapeutic effect is

experience. We have even compiled data obtained from an Internet survey that we carried out among more than 40 Spanish dermatologists working in hospital settings. In this survey, participants were questioned on their opinions regarding the management of pemphigus vulgaris (Figure 1), and we are very grateful to them for their collaboration in this endeavor.

So as not to increase the length of this article excessively, we will review the management of the most common forms of pemphigus, bullous pemphigoid and mucosal and gestational pemphigoid, linear immunoglobulin (Ig) A dermatosis, and dermatitis herpetiformis, which we considered important to include despite its multifactorial pathogenesis. We are aware that other entities (infantile, drug-related, paraneoplastic, clinical variants, etc) could be included, but it is likely that the review would then be of less practical use.

obtained at 6 to 10 weeks, and measures should be taken to prevent interaction with allopurinol, captopril, oral anticoagulants, etc. The most common side effects are gastrointestinal complaints, though the weak carcinogenic potential of the drug should not be forgotten.

Mycophenolate

Mycophenolate mofetil (CellCept capsules, 250-500 mg) is also an inhibitor of deoxynucleotide synthesis that displays good results in pemphigus vulgaris when administered orally (40 mg/kg/d in 2 doses). Its efficacy is observed after 3 to 6 months of treatment. It often causes gastrointestinal complaints, fatigue, and on occasions, lymphopenia and myelosuppression. It is less hepatotoxic than azathioprine. The drug can be requested for compassionate use.

Cyclophosphamide

Cyclophosphamide (Genoxal capsules, 50 mg, and vials, 1 g; Table 1) is an orally or intravenously administered alkylating agent that is metabolized by cytochrome P450. The oral dose varies between 1 and 3 mg/kg/d (maximum of 200 mg/d) and a therapeutic effect is observed after 4 to 10 weeks. It is more toxic than azathioprine, though also slightly more effective. It causes frequent and sometimes serious side effects—leukopenia, sometimes very severe, particularly around the 6th to 14th day of intravenous administration (Table 2); hemorrhagic cystitis due to its metabolite acrolein; azoospermia and ovarian insufficiency that are irreversible beyond a total dose of 4 to 5 g; and increased risk of bladder cancer (16%-30% of patients with Wegener granulomatosis treated over long periods), for which treatment should be accompanied with forced oral hydration (up to 3 L/d) and hematuria ruled out. Oral ulcers, nephrotoxicity, and hepatotoxicity also occur, as on rare occasions does pulmonary fibrosis.

Intravenous Immunoglobulin

Intravenous immunoglobulin, obtained from the plasma of 1000-6000 healthy donors, acts through a variety of mechanisms (> 19 pathogenic pathways). In pemphigus vulgaris it may neutralize antibodies by increasing their rate of catabolism. There are various preparations that differ in their mode of extraction, quantity of IgA, impurities, etc, and it is therefore recommended that the product is not changed once treatment has been initiated. Analysis of IgA concentration should be requested in case of deficit, which would increase the likelihood of anaphylaxis. The treatment has a half-life of 21 days, which should therefore be the interval between cycles (Table 1). Intravenous

Table 1. Treatment With Nonspecific Intravenous Immunoglobulins

Compassionate use
Diagnosis of bullous disease with complications associated with corticosteroids or a lack of response to immunosuppressive drugs
Request analysis of immunoglobulin A (risk of anaphylaxis)
Always use the same preparation (in our case, Flebogamma 10 g)
Dose, 0.4 g/kg/d for 5 days (2 g/kg); 3-4 vials per day
Repeat every 21 days and then extend the period between cycles if no lesions appear:
<ul style="list-style-type: none"> Premedicate with dexchlorpheniramine and paracetamol 1 hour before Slow infusion (6 hours) starting with 15 mL/min for 15 minutes

Table 2. Treatment With Intravenous Cyclophosphamide (Genoxal)

1. Carry out diagnosis and assessment of bullous disease
2. Begin with oral cyclophosphamide at 50 mg every 12 hours and monitor tolerance by laboratory analysis (suspend treatment if a white cell count < 2500 cells/mm ³ is observed)
3. Intravenous treatment
<ul style="list-style-type: none"> a. Dose every 15-30 days b. 1-1.5 g/m²; infusion in 200 mL over 2 hours c. Hydration with saline (500 mL in 3 hours) after the infusion. Drink abundant fluids for 3 days (from the day prior to infusion) d. Ondansetron, 1 ampule prior to infusion and another at 4 hours; if nausea continues, 8 mg orally e. Mesna, 1 ampule prior to infusion and another at 4 hours f. Cycles, 3 to 10 according to response
4. Follow-up with complete blood count, urinalysis, and monitoring of nausea/vomiting and infections
5. Corticosteroid dosage established according to clinical course

immunoglobulin has been used in a variety of autoimmune diseases and has a rapid effect, although numerous side effects have been reported, including thrombosis, acute renal failure, and anaphylaxis; the most common are headaches and nausea, and these are dependent on the rate of infusion.

Methotrexate

Methotrexate is a folic acid antagonist and has been used as a steroid sparer at low doses (7.5-15 mg/wk) in

Table 3. Treatment With Rituximab (Mabthera)

1. Diagnosis of bullous disease, resistant to other systemic treatments
2. Compassionate use
3. Prior to treatment
a. Hepatitis C virus serology
b. Antibodies (indirect immunofluorescence, enzyme-linked immunosorbent assay)
4. Dose, 375 mg/m ² (600-650 mg)
a. One day a week
b. Four weeks
c. Some use intravenous immunoglobulin 0.4 g/kg the day before (infection prophylaxis)
d. In case of relapse, a single dose according to clinical course
5. Premedicate with 1 ampule of dexchlorpheniramine and 1 g intravenous paracetamol 1 hour before
6. Slow infusion (6 hours) beginning at 15 mL/min for 15 minutes
7. In our case, we administer intravenous immunoglobulin 0.4 g/kg in the outpatient department once a month for a year.

Table 4. Treatment With Sulfone (Dapsone)

1. Request prior analysis of glucose-6-phosphate dehydrogenase, complete blood count, reticulocytes, and biochemical analysis
2. Begin at low doses (50 mg/d) and increase slowly according to patient tolerance up to a dose of 200 mg/d
3. Add vitamin E (800 IU/d) or cimetidine (1-2 g/d), optional
4. Divide the dose of dapsone into 2 fractions
5. Request complete blood count and biochemical analysis every 15-30 days for the first 3 months and every 3 months thereafter
Monitor methemoglobinemia (dizziness, dyspnea, fatigue): < 20%, no changes necessary; > 30%, consider use of methylene blue
Monitor hypersensitivity reaction, with hepatitis, erythroderma, < 500 neutrophils, peripheral neuropathy
Other: psychosis, nephrotic syndrome, blurred vision
Interaction with trimethoprim, antimalarial drugs such as chloroquine
Do not use during pregnancy, while breastfeeding, or in patients with renal or liver failure

combination with folic acid in psoriasis, but at higher doses, serious infections and side effects have been observed. In 1996 a metaanalysis advised against its use in pemphigus vulgaris. Nevertheless, some Spanish

dermatologists use it on occasions, and it is the steroid sparer advocated by the British Association of Dermatologists, even representing the preferred drug of some prestigious British authors.

Rituximab

Rituximab is a monoclonal antibody against CD20, which is expressed in mature B cells and pre-B cells; therefore, the drug does not affect stem cells or plasma cells. As a consequence, the effect is delayed by around 1 month but lasts 9-12 months, until the pathogenic B lymphocyte clone recovers, although cases have been reported in which the period without relapse was longer. It is used in an increasing number of autoimmune diseases, and the greatest risk is of severe opportunistic or nonopportunistic infections and of hypoglobulinemia (Table 3).

Sulfone

Dapsone (oral sulfone, 100 mg) has a poorly understood mechanism of action, but it is thought to be anti-inflammatory, since it can inhibit adhesion of neutrophils to the vascular endothelium, chemotaxis, lipooxygenase production, and the action of neutrophil and eosinophil myeloperoxidase (Table 4). The undesirable hematologic effects of dapsone (hemolysis and methemoglobinemia) are dose dependent (almost all occurring at doses above 150 mg/d and few below 100 mg/d) and are tolerable to some extent without it always being necessary to discontinue treatment.

Tetracyclines and Nicotinamide

In addition to their bacteriocidal and bacteriostatic effects, certain antibiotics, including tetracycline and erythromycin derivatives, also have an anti-inflammatory action. This has allowed them to be used in processes that are triggered by immunologic mechanisms. In addition, the absence of serious side effects has allowed them to be used in elderly patients. Tetracyclines have been observed to inhibit neutrophil and eosinophil chemotaxis, and they also inhibit the action of certain metalloproteinases. These 2 actions have allowed their use in elderly patients with bullous pemphigoid.

Tetracyclines tend to be used in combination with nicotinamide due to its inhibitory action at different key points in the inflammatory response, such as chemotaxis, adhesion of inflammatory cells to the endothelium, blood vessel permeability, and the release of certain proteolytic enzymes from inflammatory cells.

Pemphigus Vulgaris

At the time of writing, full consensus has not been reached on the treatment of pemphigus, since reviews on treatment disagree on certain points,³ most notably the following:

1. Pemphigus is an infrequent disease, with 1.5 cases per million inhabitants in European populations and 1.6 per 100 000 in countries such as Israel. The term pemphigus encompasses different clinical forms: pemphigus vulgaris and its vegetative form; pemphigus foliaceus or seborrheic pemphigus, with a geographic variant in South America and Tunisia (endemic pemphigus); and rare forms such as paraneoplastic pemphigus, pemphigus herpetiformis, and IgA pemphigus. Since they are so infrequent, the number of clearly defined cases considered in published series never exceeds 50, and this presents difficulties in assigning randomized groups with conclusive results.^{4,5} Some articles report cases diagnosed with pemphigus vulgaris on the basis of symptoms and histology alone and without the use of any type of immunofluorescence.
2. The severity of pemphigus can vary even within individuals. Efforts have been made to develop a scale for the measurement of severity similar to the Psoriasis Area Severity Index,⁶ covering criteria such as the rule of 9's, the extent of erosion or dry crust, and tolerated foods (the so-called autoimmune bullous skin disorder intensity score), with good intentions but little practical use. Severity is also classified as mild, moderate, and severe according to the judgment of the observer. The disease continues to be associated with a mortality of 5%, usually as a result of treatment complications.
3. There are no clear criteria regarding cure or remission. Some authors define them on the basis of indirect or direct immunofluorescence, others on the basis of symptoms or the requirement for immunosuppressive therapy. One of the criteria used is the absence of lesions for 3 months, but this is inconsistent with clinical experience with these patients. In Spain, we tend to refer to remission when the patient has not presented lesions in a year without the need for oral drug treatment. Given the extent of this variability in the criteria used, complete remission of patients with pemphigus vulgaris has been reported at up to 50% at 5 years and 75% at 10 years, data that we consider a little optimistic. It has also been reported that 17% of cases of pemphigus vulgaris respond rapidly and with a good prognosis (entering remission), compared with 35% of cases with continuous outbreaks, but this was based on a series of 44 patients.
4. There are clear differences in the treatment criteria applied according to geographic region, and even within the same region. Thus, in Japan, case series have been published involving treatment with plasmapheresis, while this is not so widely used in Europe. Some experts in the treatment of pemphigus report methotrexate to be their favored steroid-

sparing drug, while others rule out its use. Furthermore, since the inclusion criteria for the different studies vary, there are no meta-analyses or systematic reviews available. At the time of writing, most articles tend to conclude that dermatologists should treat pemphigus in whatever way their experience tells them to, even talking of the "art of treatment" in pemphigus. For instance, some British authors prefer methotrexate while others from the same country favor dapsone. We will offer some guidelines based on the experience of various Spanish hospitals that regularly treat bullous diseases and supported by a survey of more than 40 hospital-based dermatologists.

5. There is an initial enthusiasm for the use of new treatments, but over time these ultimately find their place in relation to specific indications. Reports have been published of remission occurring with 1 to 3 cycles of intravenous immunoglobulin, mycophenolate mofetil indicated as monotherapy without corticosteroids, ablative pulses of cyclophosphamide with serious side effects, and plasmapheresis and its variants, but only in highly selected cases. Furthermore, the means available for treatment of patients vary according to dermatologist and hospital.
6. The only common guideline is to initiate treatment of pemphigus vulgaris with corticosteroids until the disease is controlled. But then differences appear concerning whether a more effective corticosteroid is available, how to taper the dose, whether an immunosuppressive drug should be added from the outset, and if so, which one.

Diagnosis

The following criteria should be applied in the diagnosis of any type of pemphigus⁷:

1. Compatible symptoms: blisters, erosions, and crusts, sometimes along with detachment of the skin when rubbed.
2. Diagnostic histopathology: acantholysis of the suprabasal layer in pemphigus vulgaris and the granular layer in pemphigus foliaceus, or the characteristic criteria applicable in less common clinical forms. Biopsy is preferably taken from a small intact vesicle.
3. Direct immunofluorescence positive for IgG (sometimes complement or IgA). Biopsy of healthy perilesional skin.
4. Presence of circulating antibodies against desmogleins, measured by titrated indirect immunofluorescence or ELISA. Both techniques are highly specific, but ELISA is slightly more sensitive. They parallel clinical activity and so should be requested during treatment. These criteria should be met for a diagnosis of pemphigus vulgaris or pemphigus foliaceus (the most common forms). When faced with a case of paraneoplastic pemphigus, the relevant antigen should be detected by direct immunofluorescence.

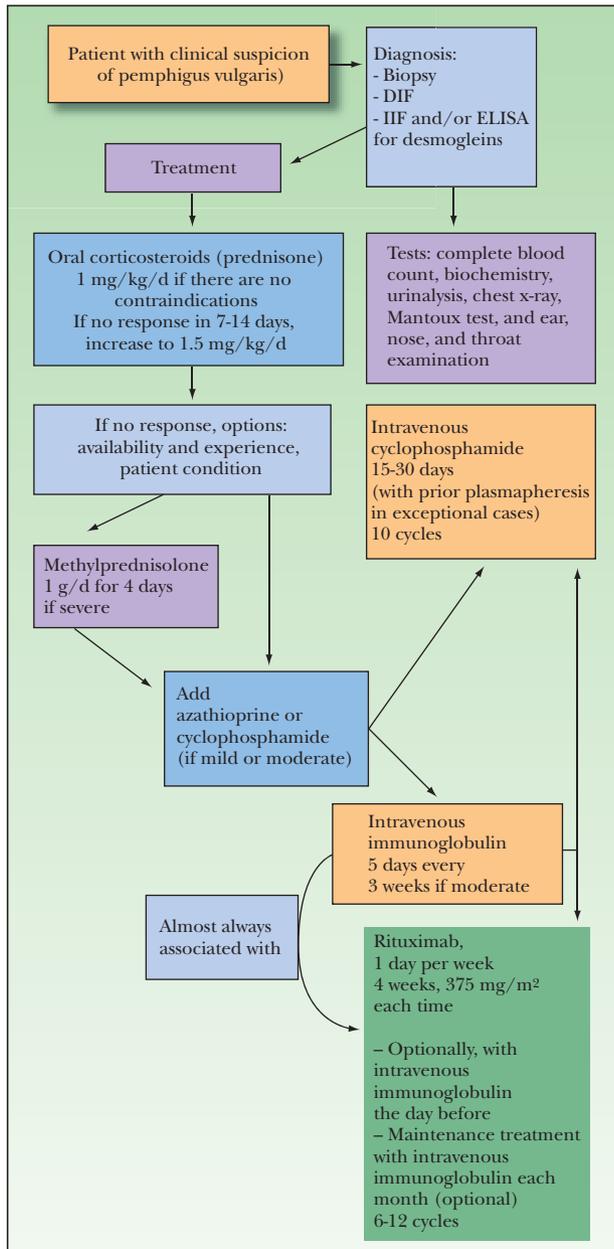


Figure 3. Treatment algorithm for pemphigus vulgaris. DIF indicates direct immunofluorescence; ELISA, enzyme-linked immunosorbent assay; IIF, indirect immunofluorescence.

During research or description of new entities, the antigen involved should be studied (immunoblotting and immunoprecipitation) along with the immunoglobulin subtype involved, etc.

In addition to standard laboratory workup, we should analyze ear, nose, and throat symptoms, carry out a Mantoux test and chest x-ray, and assess hepatitis serology to prevent reactivation with treatment.

Treatment

Corticosteroids continue to be the initial treatment of choice (Figure 3). The type of corticosteroid varies, but in Spain the most commonly used is oral prednisone at a dose of 1 mg/kg/d taken with breakfast, and the dose would be increased to 1.5 mg/kg/d if the condition were not controlled within 10 days.⁸ From this point on there is less agreement—some continue to increase the dose to 2, 3, or 4 mg/kg/d, but we prefer to introduce a rapid-onset alternative such as intravenous immunoglobulin, 2 g/kg, or sometimes pulses of cyclophosphamide every 15 to 30 days. Once the outbreak is controlled, progressive reduction of prednisone is initiated, with no strict regimen (8–12 weeks), until a maintenance dose of 15–20 mg/d is reached and efforts can be made to provide the drug on alternate days. An immunosuppressive drug is preferably added from the outset, or if not, it should be prescribed upon recurrence of lesions, at which point reduction of the corticosteroid dose should also be stopped.

In severe cases in which the disease is not controlled, intravenous dexamethasone or methylprednisolone (1 g/d, 4 days) can be provided in a slow infusion over 3 to 4 hours. It should be avoided in the elderly and in cases of multiple disease due the risk of convulsions, hypertension, heart disease, electrolyte imbalance, psychosis, neuropathy, and pancreatitis.

Recalcitrant lesions of the oral mucosa have been treated with intralesional triamcinolone, or more often, clobetasol propionate, 0.05% in Orabase, according to the efficacy that is also observed in isolated cutaneous lesions with high-potency corticosteroids.

The most common steroid-sparing immunosuppressive drug is azathioprine at a dose of 50 mg every 12 hours,⁹ but it is best to adjust the dose according to the enzyme that metabolizes the drug. The association of immunosuppressive therapy in pemphigus vulgaris would seem to be justified on the basis of the relapses that occur when the corticosteroid dose is reduced.¹⁰

Another immunosuppressive drug that is available for compassionate use in Spain is mycophenolate mofetil at doses between 1 and 3.5 g/d; it has a slow onset of action and is frequently associated with gastrointestinal complaints.^{11–13} The drug has been reported to be highly useful in series of patients with pemphigus vulgaris, but its bioavailability is irregular and its results therefore variable.^{14,15}

Cyclophosphamide has been found to be useful for the treatment of pemphigus vulgaris both orally (50 mg every 12 hours) and intravenously (1.5–2.5 mg/kg/d).^{16,17} It has numerous side effects, as mentioned. It has been employed more effectively in pulses every 15 or 30 days (varying dose from 1 g/m², though 5–10 mg/kg per cycle is most effective). It is administered with antiemetics and mesna in an effort to prevent hemorrhagic cystitis. Between 5 and 10 prior sessions of plasmapheresis can also be used to reduce the levels of antibodies. General malaise with vomiting,

myelosuppression, alopecia, etc, can also occur, but the efficacy of the drug has been confirmed on numerous occasions.

Prior to 2005 there were less than 100 published cases of intravenous immunoglobulin to treat pemphigus vulgaris using a consensus protocol in which the length of time between cycles is slowly increased (up to 16 weeks) once disease control and improvement are achieved. Once a period of 4 months without relapse has passed, suspension of treatment can be attempted.¹⁸⁻²⁰

Tolerance is very good with slow infusion in a day hospital over 6 hours per cycle, premedicating with H1 antihistamines and paracetamol. More rapid infusion has been associated with side effects including headaches, hypertension, nausea, and myalgia, and less often with thrombosis, anaphylaxis, renal insufficiency, and heart failure.²¹⁻²³

The standard dose we use is 0.4 g/kg/d over 5 days (2 g/kg in total) repeated every 21 days as monotherapy, although increasingly often with associated treatment directed against the lymphocyte clone (rituximab or on occasions cyclophosphamide administered as a bolus). We have observed a rapid effect that allows the dose of corticosteroids to be reduced, but numerous cycles are required (15 to 30), in contrast to some initial optimistic reports of satisfactory outcomes with 1 to 3 cycles. As a result, the cost increases disproportionately (compassionate use). We have analyzed antibodies before and after treatment cycles and found no reduction despite clinical improvement being observed. As a result, we have more recently been using 4 cycles of rituximab almost exclusively (8 patients), with excellent results. We believe this approach is indicated in patients in whom disease is not controlled despite high doses of corticosteroids or in whom corticosteroids are contraindicated (due to glaucoma, poorly controlled diabetes, tuberculosis, etc), and treatment should perhaps be provided in combination with an immunosuppressive drug.²⁴

Plasmapheresis is now rarely used except in Japan. It is used in severe and acute cases, in those in which other treatments are contraindicated, and in those with a high concentration of circulating antibodies, since these are extracted from the blood during filtration. Its main drawback, in addition to its limited availability, is the early rebound effect from the second to the fifth day, which should be halted with pulses of cyclophosphamide, since oral immunosuppressants or intravenous immunoglobulin are not usually sufficient.^{25,26} Side effects are not uncommon, since between 2 and 5 L of blood are extracted, filtered, and plasma replaced with a substitute. There is a risk of thrombosis, infection, and a requirement for arteriovenous fistulas. It is also a very expensive procedure. We have used it in various patients in collaboration with the nephrology department and obtained good initial results, but with a marked rebound effect that has led us to gradually stop using the technique. In Spain, plasmapheresis seems only to be used in exceptional cases.

Other apheresis techniques based on plasmapheresis and involving extraction of pathogenic antibodies have been used. These include specific immunoabsorption and even

extracorporeal photopheresis with exposure of serum to psoralens and UV-A.

When used, 5 to 10 sessions of plasmapheresis are carried out, followed the day after the final cycle with an intravenous bolus of cyclophosphamide.²⁷⁻³⁰

More than 40 cases have now been published in which rituximab has been used, and positive results have been obtained in 88%, with minimal side effects. The dose is the same as that used in other diseases such as B-cell lymphoma: 375 mg/m²/wk for 4 weeks.

In pemphigus vulgaris, 2 cycles have been administered in cases of resistance, or in other cases isolated infusions with a single day's dose in cases of relapse. We often combine treatment with monthly intravenous immunoglobulin at a dose of 0.4 mg/kg for 10 to 12 months in order to prevent infections and help with early therapeutic effectiveness by neutralizing circulating antibodies, for which rituximab is ineffective. Severe opportunistic infections have been described³¹ but these have not occurred in the 8 cases we have treated.

Other treatments used in pemphigus vulgaris include high-dose cyclosporin, which does not have clearly demonstrable efficacy compared with corticosteroids alone³²⁻³⁴; dapsone may be best reserved for mild pemphigus with predominance of neutrophils (IgA, herpetiformis, etc). Some authors support its use from the outset, but with a high rate of failure in the control of pemphigus. The traditional treatment of gold salts can be administered orally or intramuscularly. Some years ago they were more extensively used, but the side effects (both renal and cutaneous) that appear in up to 30% of patients have relegated their status to that of a third-line treatment in cases of immunosuppression, in young patients, etc. Their onset of action is slow.

Infliximab, chlorambucil, tetracyclines, nicotinamide, and pyridostigmine have also been used in isolated cases.^{35,36}

Treatment in Other Forms of Pemphigus

The treatment options do not differ for pemphigus foliaceus, except that it is usually (not always) less resistant to treatment and prednisone can be started at an initial dose of 0.5 mg/kg/d and then increased according to the response. Topical corticosteroids are more effective than in pemphigus vulgaris and immunosuppressive therapy is not always necessary. In our experience, intravenous therapy has almost never been required, but this can be used if remission is not achieved. Since other variants of pemphigus are much less common we will not discuss them here.

Bullous Pemphigoid

As in other bullous autoimmune disease, there is no agreement regarding the management of patients with

bullous pemphigoid.³⁷ However, in general terms, this bullous disease tends to be less severe than pemphigus vulgaris,³⁸ and morbidity is generally lower than in other diseases such as mucosal pemphigoid or acquired epidermolysis bullosa. As a result, the treatment required in bullous pemphigoid is less aggressive and should focus more on the inflammatory component than on the production of autoantibodies, as in the management of pemphigus vulgaris.

Certain factors should be taken into consideration in order to better understand this disease and adequately assess each patient^{39,40}:

1. Bullous pemphigoid is an autoimmune bullous disease with a higher incidence in Spain, estimated at between 0.7 and 1.8 new cases per 100 000 inhabitants per year, particularly in those aged over 75 years.
2. Clinically, patients display generalized pruritus. Subsequently, infiltrated erythematous lesions can develop upon which bullous lesions may appear; these lesions contain clear fluid and can become hemorrhagic. They mainly occur on the lower trunk, skin folds, and flexor surfaces of the limbs. The lesions do not leave scars and rarely affect the head and neck. Only on rare occasions do they initially appear in localized forms on the limbs and then subsequently spread, begin as dyshidrosiform lesions on the distal extremities, or appear as erythematous nodules (pemphigoid nodularis).
3. It is important to be aware that there are 2 components defined in bullous pemphigoid. Patients present IgG antibodies against proteins in the dermal-epidermal junction, specifically against hemidesmosome proteins, particularly BP180. In addition, there is a more marked inflammatory component than in pemphigus vulgaris in which the action of neutrophils activated by the Fc fraction of the autoantibodies causes release of proteolytic enzymes that damage the dermal-epidermal junction.
4. There are no clearly defined criteria that can be used to determine how and when treatment should be varied in a patient with bullous pemphigoid. Nevertheless, unlike in other diseases such as pemphigus vulgaris, bullous pemphigoid is often a self-limiting disease, though it can last a few months or even years. Another important factor in establishing key points of reference for the management of bullous pemphigoid is the absence of defined analytic variables that provide objective information on the condition of each patient. The most widely used criterion is the clinical course. In addition to this information, it is particularly helpful to analyze circulating antibodies against the epidermal basement membrane by indirect immunofluorescence with monkey esophagus or selective determination of circulating antibodies against BP180, one of the antigens implicated in bullous pemphigoid. Nevertheless, no studies are available in which the

relationship between improvement of patient condition and the titer of these circulating antibodies is assessed.

5. As in pemphigus, mainly pemphigus vulgaris, the development of new therapies has often diverted attention toward their use in bullous pemphigoid. Nevertheless, it should not be forgotten that many of these treatments have not been shown to be more effective than other more traditional and less expensive ones for which more experience is available.
6. Patients with bullous pemphigoid come from a section of the population with certain characteristics that should be taken into consideration. They tend to be elderly individuals, many of whom receive multiple treatments. This is particularly important, since some cases of bullous pemphigoid are drug induced. Secondly, since the patients tend to be older, their metabolism and immune system are more fragile, thus increasing the risk of side effects due to treatment. Broadly speaking, we use local corticosteroids in all cases of localized lesions. In addition, studies have shown that administration of immunoregulatory or even anti-inflammatory drugs may be effective.

Diagnosis

As mentioned, the appearance of the lesions and their location, as well as the presence of pruritus, are the main diagnostic factors for bullous pemphigoid.⁴¹

Histopathology reveals the presence of subepidermal blistering along with an inflammatory infiltrate in the dermis that is rich in eosinophils and sometimes neutrophils. Eosinophilic spongiosis is apparent in early lesions.

Direct immunofluorescence of the perilesional skin reveals linear deposits of C3 at the dermal-epidermal junction in more than 90% of cases. In addition, deposits of IgG (in up to 80% of cases) or, less often, IgM and IgA (around 15% of cases) are observed in the same location.

Indirect immunofluorescence can be used to detect circulating antibodies against the antigens at the dermal-epidermal junction. If we use monkey esophagus as a substrate, these antibodies can be detected in 80% of patients. Use of the salt-split skin technique in human skin increases the percentage of samples in which antibodies are detected to up to almost 80%, with the deposits detected mainly on the epidermal side of the split.

If ELISA is available, circulating antibodies against BP180 can be detected in almost all patients. Immunoblotting reveals antibodies against the NC16A portion of the bullous pemphigoid antigen.

Of the treatment algorithms that have been published on the management of patients with bullous pemphigoid, we feel that the one proposed by Mutasim is appropriate (Figure 4). The algorithm centers treatment on whether the lesions are mild to moderate or instead are extensive.

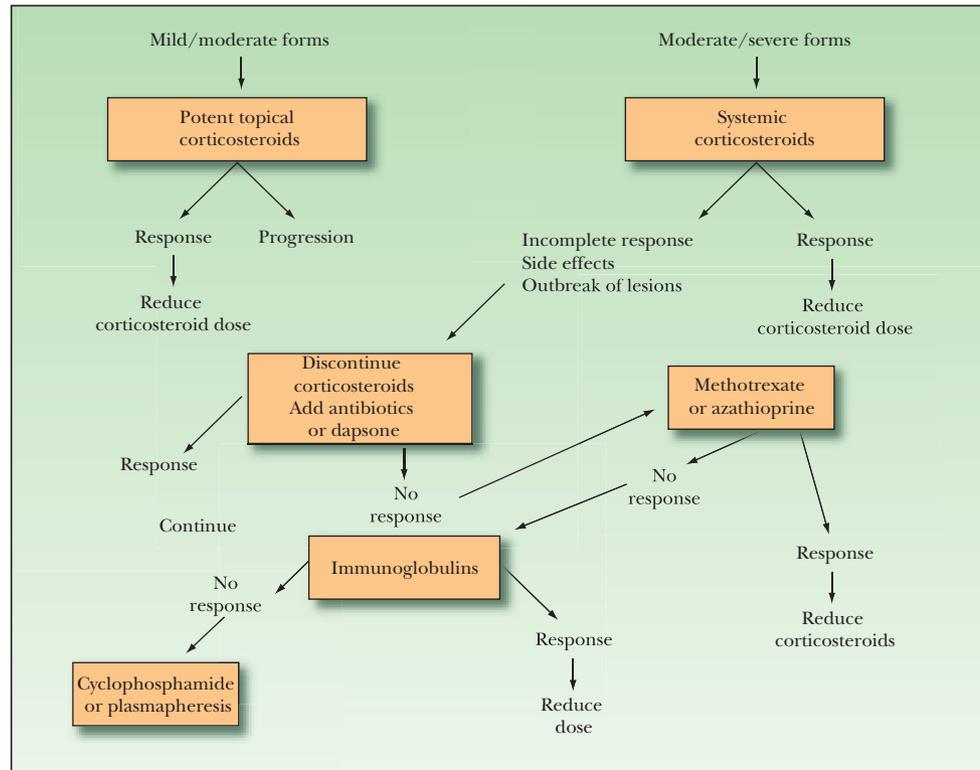


Figure 4. Treatment of bullous pemphigoid.

In patients with mild or moderate disease, potent corticosteroids can be used initially. Recent studies have shown that the use of clobetasol propionate (40 g/d) allows control of the disease in most patients with extensive disease compared with a group of patients who received oral prednisone (1 mg/kg/d), in which the percentage of patients in whom the disease was controlled in a similar period of time was slightly lower.^{42,43} In addition, there were benefits in terms of side effects and survival in the group of patients who received topical treatment. If the disease is not controlled, systemic corticosteroids should be administered.

Regarding the administration of systemic corticosteroids, studies have established various important points. Doses above 0.75 mg/kg/d do not appear to confer greater benefit than lower doses but are associated with a greater risk of serious side effects. Consequently, the recommended dose of prednisone is 0.5-0.75 mg/kg/d. A favorable response is obtained in the first 4 weeks, with marked improvement of the lesions. At this point, the dosage should be reduced. When the dose of prednisone is 30-40 mg/d a regimen of treatment on alternate days can be initiated. If a repeat outbreak of the disease occurs during dosage reduction, the dose should be increased by 10 to 20 mg/d every 2 or 3 weeks until the disease is controlled again. In many cases the lesions disappear in 6 to 10 months and prednisone treatment can be discontinued.

Dapsone can be added in those patients who present outbreaks of bullous pemphigoid lesions, in whom side effects of corticosteroid treatment begin to appear, or in

whom an adequate response is not observed. The recommended dose is between 50 and 150 mg/d.

Antibiotics can also be added,⁴⁴ mainly tetracyclines or erythromycin, associated with nicotinamide as an alternative to dapsone and under the same circumstances. This may also be the treatment of choice when corticosteroids are contraindicated or in very elderly patients. Erythromycin also tends to be recommended in children to avoid prescription of tetracyclines. The dose of tetracyclines is 500 mg 4 times daily and nicotinamide is used at a dose of 500 mg 3 times daily. Doxycycline has also been used at a dose of 100 mg twice daily. When erythromycin is used it should be at a dose of 1-3 g/d. Once the number of lesions has been controlled, the dose of associated corticosteroids can be reduced until they can even be discontinued, and the dose of nicotinamide and antibiotics reduced afterwards.

When the patient presents side effects due to corticosteroid treatment and the disease is also not controlled at high doses, administration of immunosuppressive drugs is indicated. More experience has been gained with azathioprine, with good results. It can be used at a dose of up to 2.5 mg/kg/d, and always in association with prednisone. Nevertheless, some studies have suggested that it could have a similar efficacy in bullous pemphigoid as monotherapy or as a steroid sparer. Methotrexate at a dose of 5-15 mg/wk is not as effective in bullous pemphigoid. It is more often prescribed in patients with associated psoriasis lesions. Unlike in other autoimmune diseases,

insufficient information is available regarding treatment with mycophenolate mofetil.

If patients do not show improvement with a combination of prednisone and azathioprine, or we do not succeed in reducing the dose of corticosteroids without recurrence of lesions, administration of intravenous immunoglobulin should be assessed; this is a very expensive drug that is usually recommended at a dose of 2 g/kg in cycles of 3 to 5 consecutive days, with patients receiving 2 to 4 cycles at 3 or 4 week intervals.

If the lesions are not controlled following addition of intravenous immunoglobulin, we recommend administration of cyclophosphamide. This can be given orally or via intravenous bolus. Oral cyclophosphamide is usually given at a dose of 1 to 2 mg/kg/d. However, there are few reports of its use available in the literature.

Gestational Pemphigoid

Gestational pemphigoid, also known as herpes gestationis, is an autoimmune bullous disease that occurs in 1 in 20 000 to 50 000 term pregnancies,⁴⁵ usually developing in the second or third trimester or in the postpartum period. It is accompanied by severe pruritus that appears some weeks before the development of blisters along with urticarial plaques and papules. It usually begins on the abdomen before spreading to more generalized areas, including the palms and soles. Mucosal involvement is rare, and patients sometimes present other autoimmune conditions (thyroiditis, alopecia areata, etc).⁴⁶

Pathology reveals subepidermal blistering with eosinophils, sometimes forming small abscesses in dermal papillae or as eosinophilic spongiosis. Direct immunofluorescence revealing deposits of C3 (sometimes with IgG) in the basement membrane is essential for diagnosis. Salt-split skin reveals C3-binding circulating IgG in more than 90% of cases. Conventional techniques only result in detection of 20% of cases. ELISA reveals the presence of anti-BP180 antibodies in 90% of cases, and the presence of these antibodies appears to be linked to disease activity.

It is essential to differentiate the disease from polymorphous eruption of pregnancy (1 in 300 pregnancies), which is clinically similar but does not involve blistering. Therefore, direct or indirect immunofluorescence must be used in the diagnosis.

Prognosis involves resolution of the disease within a few weeks of giving birth, but the risk of more aggressive recurrence in subsequent pregnancies is 92%. Oral contraceptives can lead to recurrence in 15% to 50% of cases. The disease appears not to be associated with increased fetal mortality, but there is a higher percentage of preterm and low-weight births. There is no consensus regarding the recommendation or prohibition of breastfeeding.⁴⁷

Therapeutic management involves the following:

1. Alleviation of pruritus (dexchlorpheniramine)
2. Use of corticosteroids—topical in mild cases and systemic (0.3-0.5 mg/kg/d prednisone) in almost 80% of cases. The pregnancy should be considered high risk and gynecologic monitoring provided.
3. On rare occasions, other therapies such as immunosuppressive drugs, intravenous immunoglobulin, and cyclosporin have been used.

Mucosal Pemphigoid

Mucosal pemphigoid was previously known as cicatricial pemphigoid, oral or ocular pemphigoid, or benign mucosal pemphigoid.⁴⁸ It is probably a combination of various diseases with a similar phenotype but in which a variety of antigens are involved (BP180 most often; integrin $\alpha 6\beta 4$, which is strongly implicated in the pathogenesis; laminin 5 and 6; collagen VII; uncein; a 45 kDa protein; a 168 kDa protein; and a 120 kDa protein). It affects various mucosas (ocular [50%-70%], gingival [85%], buccal, nasal [15%], genital and anal [15%], pharyngeal, laryngeal, esophageal, etc) with erythema, erosions, blisters, and subsequent scars that can cause symblepharon, entropion, and trichiasis with abrasion and perforation of the cornea leading to blindness. The skin is usually unaffected. In other mucosas it can cause bleeding, odynophagia, dysphonia, and dysphagia.⁴⁹

Diagnosis

1. Compatible signs and symptoms⁵⁰
2. Pathology, which is sometimes hindered by difficulty and absence of acute lesions. Subepidermal blistering can be seen with a mixed infiltrate containing eosinophils.
3. Direct immunofluorescence is best in the oral mucosa. IgG, IgA, and C3 seen in the basement membrane.
4. Indirect immunofluorescence is best in salt-split skin after 24-48 hours; staining is seen on the epidermal side. ELISA reveals the presence of anti-BP180 antibodies, among others.

Treatment

Treatment centers on 3 points, based on interventions involving dermatologists, ophthalmologists, and ear, nose, and throat specialists, among others⁵¹:

1. Reducing antibody production
2. Reducing inflammation
3. Preventing sequelae

Patients who are at low risk (only oral and mild cutaneous involvement) should maintain good oral hygiene and receive topical corticosteroids and sometimes oral dapsone. If no improvement is observed, low-dose oral corticosteroids can be added. In patients at high risk (ocular, nasopharyngeal, genital, and esophageal involvement), dapsone is initiated in combination with prednisone 1 mg/kg/d, and if no improvement is observed, cyclophosphamide boluses are administered (3 to 10 boluses) along with oral cyclophosphamide. There have been reports of improvement with mycophenolate mofetil, rituximab, and conjunctival mitomycin. As mentioned, management should involve a multidisciplinary team.

Dermatitis Herpetiformis

Dermatitis herpetiformis is an autoimmune bullous disease that appears as a cutaneous manifestation of gluten intolerance.⁵² It forms part of a spectrum of diseases that have sensitivity to gluten in common, including celiac disease and gluten ataxia. It is thought that around 5% of patients with celiac disease develop dermatitis herpetiformis during their lifetime. All patients with the disease are sensitive to gluten, but the vast majority do not develop gastrointestinal symptoms. In a recent case series involving 300 patients with dermatitis herpetiformis, only 13% had gastrointestinal symptoms. In the remaining cases, only intestinal biopsy can lead to diagnosis of gluten-sensitive enteropathy. In the various case series published, between 60% and 75% of patients with dermatitis herpetiformis display histopathologic abnormalities in the intestinal biopsy.^{53,54}

The eruption is highly pruriginous and is typically distributed on the extensor surfaces, posterior surface of the forearms, and the buttocks. The cutaneous lesions consist of erythematous papules, small vesicles, and excoriations. Intact vesicles may be difficult to find, and the occurrence of frank blisters is rare, thus presenting difficulties in arriving at a diagnosis.

Analysis of skin biopsies reveals microabscesses containing neutrophils in the papillary tips,⁵⁵ variable inflammatory infiltrates in the superficial dermis, and occasionally subepidermal vesicles. These findings are nonspecific and are described in other autoimmune bullous diseases.

Definitive diagnosis is based on the pathognomic finding of granular IgA deposits (with or without C3) at the dermal-epidermal junction by direct immunofluorescence on samples of healthy perilesional skin. These deposits may be concentrated in the tips of the dermal papillae. The sensitivity of this test is around 90% to 95%.

The endomysial self-antigens specifically recognized in both diseases have recently been identified as tissue transglutaminase (TGt) in celiac disease and epidermal transglutaminase (TGe) in herpetiform dermatitis.⁵⁶⁻⁵⁸

IgA autoantibodies against smooth muscle endomysium are highly specific for gluten-sensitive enteropathy (patients with celiac disease or dermatitis herpetiformis). These autoantibodies are present in more than 70% of patients with dermatitis herpetiformis who follow a normal diet (containing gluten).⁵⁹

All these antibodies (IgA anti-endomysium, IgA anti-TGt, and IgA anti-TGe) are significantly reduced by a gluten-free diet and are therefore useful not only for diagnosis but also for follow-up in patients with gluten-sensitive enteropathy.^{60,61}

Anti-reticulin and anti-gliadin antibodies can also be detected. IgA anti-reticulin antibodies are highly specific and are found in 1 out of every 4 patients with dermatitis herpetiformis, as well as in patients with celiac disease; they are also reduced until they eventually disappear following initiation of a gluten-free diet. Both IgG anti-reticulin antibodies and anti-gliadin antibodies (IgA or IgG) are nonspecific and often appear in patients with other bullous autoimmune diseases, and even in healthy subjects.

In those patients with clear clinical suspicion, in whom analysis of IgA autoantibodies is negative, analysis of total IgA should be requested, since this situation may be due to selective IgA deficit. In these cases, serologic diagnosis of gluten sensitivity is obtained by determination of IgG anti-transglutaminase antibodies.

The association of dermatitis herpetiformis and lymphomas is subject to debate.^{62,63} Unlike in patients with celiac disease, in whom a correlation has been described with hematologic tumors (particularly intestinal T-cell lymphomas), the frequency of any type of lymphomas in patients with dermatitis herpetiformis is less than 2% according to available studies.⁶⁴

Therapeutic Management

Dermatitis herpetiformis is treated with a combination of a gluten-free diet and dapsone.⁶⁵

A gluten-free diet is essential in any patient with dermatitis herpetiformis. It is effective for treatment of cutaneous manifestations (and gastrointestinal ones if present), though the improvement appears later than with the use of dapsone. Foods containing wheat, barley, or rye are prohibited, but rice, maize, and oats can be eaten.^{66,67} A gluten-free diet must be observed for life, since the disease recurs upon reintroduction of gluten into the diet in the vast majority of patients with dermatitis herpetiformis. Only between 10% and 20% of patients develop immunologic tolerance and are able to maintain a normal diet after years following a strict gluten-free diet (especially infant-onset cases and patients treated at some time with dapsone).

Dapsone effectively suppresses the cutaneous manifestations of dermatitis herpetiformis within a few days. It has no effect

Table 5. Principal Characteristics of Dermatitis Herpetiformis

<i>Clinical Manifestations</i>
Intense pruritus
Papulovesicular eruption (excoriated) on the extensor surfaces and buttocks
Gastrointestinal symptoms?
<i>Skin Biopsy</i>
Papillary abscesses containing neutrophils, subepidermal separation
Granular IgA in the basement membrane (direct immunofluorescence)
<i>Immunologic Study</i>
Anti-endosome IgA antibodies
Anti-transglutaminase IgA antibodies
(Anti-reticulin IgA antibodies)
(Anti-gliadin antibodies)
<i>Gastrointestinal Study (If There Are Gastrointestinal Symptoms and Signs of Malabsorption)</i>
Assessment by a gastroenterologist
Biopsy of the mucosa of the small intestine (distal duodenum, jejunum) by fiberoptic gastroscopy
Treatment: gluten-free diet, dapsone

Abbreviation: IgA, immunoglobulin A.

on the possible intestinal disease, and there is also no evidence that it reduces the risk of developing lymphoma. It is not curative in dermatitis herpetiformis and cutaneous eruptions reappear following discontinuation of the drug.

Finally, there are various associations and networks that facilitate access to useful information for patients with celiac disease or dermatitis herpetiformis (brands of foods that are safe or prohibited, recipes, shops and restaurants, activities, information for school canteens, financial assistance, etc) (Table 5).

Linear IgA Bullous Dermatitis

As suggested by its name, linear IgA bullous dermatosis is a vesicular/bullous disease involving linear deposits of IgA along the length of the basement membrane. According to some studies undertaken in Europe (mainly France and Germany), the incidence of this disease is approximately 0.2–0.5 cases per million inhabitants per year. These figures probably underestimate the true frequency, since

immunofluorescence studies were not performed adequately.

Along with dermatitis herpetiformis, linear IgA bullous dermatosis represents the most common bullous disease in childhood, and it was previously known as chronic bullous dermatosis of childhood.

The classic characteristic presentation of linear IgA bullous dermatosis involves appearance of lesions in the form of annular or polycyclic erythematous plaques with vesicles or blisters around the edge, adopting a pattern that has been compared to a string of pearls. In many patients, however, the presentation may be completely indistinguishable from dermatitis herpetiformis or bullous pemphigoid. In drug-induced cases in particular the symptoms may be highly atypical and be more reminiscent of erythema multiforme or toxic epidermal necrolysis. It is important to remember that the mucosas are very often affected in linear IgA dermatosis, and that the appearance may be consistent with mucosal pemphigoid, with oral, ocular, nasal, genital, laryngeal, or bronchial involvement. It is therefore important to collaborate with other specialists (for instance, ophthalmologists) for appropriate management of these patients.

Another important element in the clinical assessment of patients in whom linear IgA dermatosis has been diagnosed is the identification of the various medications that the patient is taking, especially in those who have been admitted to hospital, since there is a drug-induced variant of the disease (in fact it is the most common drug-induced bullous autoimmune disease). The drug that is most often involved (more than half of all cases) is vancomycin, but other antibiotics (particularly penicillin and its derivatives), antihypertensives (angiotensin converting enzyme inhibitors), antiepileptics, lipid-lowering drugs, nonsteroidal anti-inflammatory drugs, etc, have also been implicated. In most cases the skin disease resolves upon discontinuation of the drug.

Diagnosis

Optical microscopy and immunofluorescence are required to obtain a diagnosis (Figure 5). The histology of linear IgA dermatosis is nonspecific, since it involves the presence of subepidermal vesicles containing abundant neutrophils and a variable number of eosinophils. These findings may be completely indistinguishable from those associated with dermatitis herpetiformis, bullous pemphigoid, acquired bullous epidermolysis, or bullous systemic lupus erythematosus, and histology alone is insufficient to distinguish between these different diseases. Consequently, immunofluorescence studies are required. Direct immunofluorescence in biopsies of perilesional skin reveals the presence of linear IgA deposits along the length of the basement membrane, with or without complement deposits.

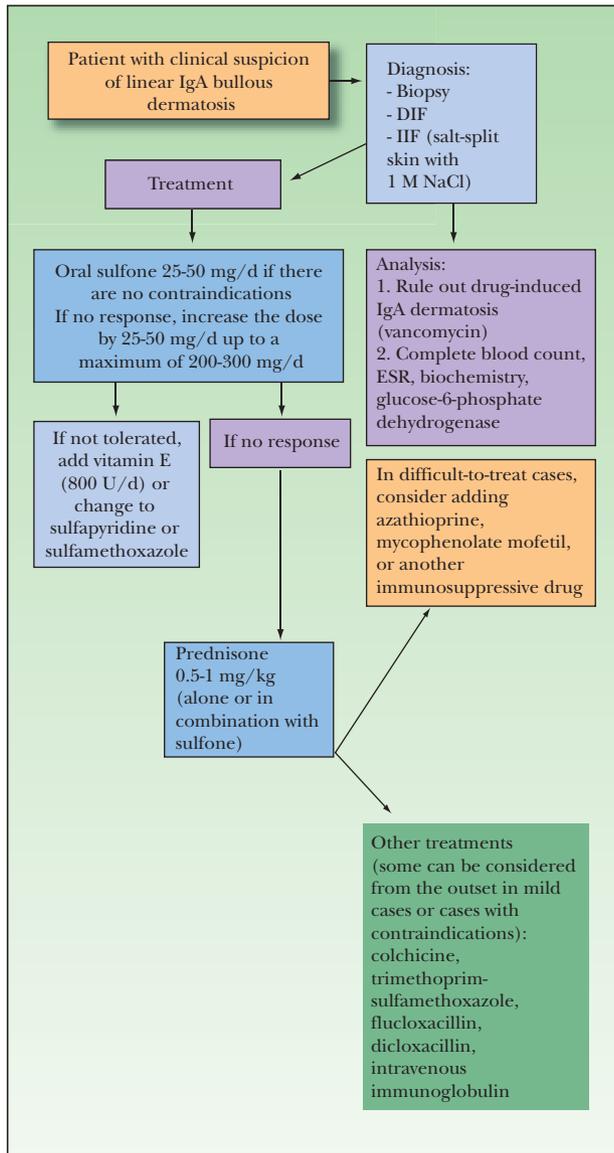


Figure 5. Treatment algorithm for linear immunoglobulin IgA bullous dermatosis. DIF indicates direct immunofluorescence; ESR, erythrocyte sedimentation rate; IgA, immunoglobulin A; IIF, indirect immunofluorescence.

There may also be IgG deposits, but these always occur at a much lower intensity than those of IgA. Otherwise, the diagnosis may correspond to other diseases such as bullous pemphigoid, acquired bullous epidermolysis, or bullous systemic lupus erythematosus. Indirect immunofluorescence can detect the presence of circulating IgA autoantibodies against the dermal-epidermal basement membrane in almost half of all patients. The titers of these autoantibodies are almost always low. The sensitivity and antibody titers are increased if salt-split skin (1 M NaCl) is used as a substrate. Antibodies from most patients (80%) bind the epidermal part (roof) of the preparation, while the remaining 20% display a dermal pattern (floor staining).

Treatment Options

Unlike in dermatitis herpetiformis, since gluten-sensitive enteropathy is not present, gluten-free diet plays no role in the management of this disease. In cases of drug-associated linear IgA dermatosis, the implicated medication should be discontinued immediately. It is also important that patients with ocular symptoms are seen by an ophthalmologist.

Sulfone

Sulfone is the treatment of choice in linear IgA dermatosis. The dose is usually between 25 and 50 mg, and is increased slowly according to clinical response and patient tolerance until a dose of 100-200 mg/d is reached (see previous section on sulfone).

Other sulfonamides such as sulfapyridine or sulfamethoxyypyridazine can also be used; despite having the same profile of side effects, they tend to be better tolerated.

Cases that do not respond to sulfone should be treated with systemic corticosteroids such as prednisone (0.5-1 mg/kg/d). Corticosteroids can be administered alone or in combination with sulfone (if tolerated by the patient). In some cases the use of immunosuppressive drugs (azathioprine, mycophenolate mofetil, etc) may be necessary, and the results are good, although there is no established regimen and the same regimen as for pemphigus vulgaris should be used.

Conflicts of Interest

The authors declare no conflicts of interest.

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