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Treatment of subepidermal immunobullous diseases

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Abstract

The subepidermal immunobullous diseases are a group of autoimmune blistering disorders of the skin and mucous membranes that share the common features of autoantibody deposition and blister formation at the dermal-epidermal junction or basement membrane. This group includes bullous pemphigoid, linear IgA disease, dermatitis herpetiformis, and epidermolysis bullosa acquisita, among others. Although these disorders share some common features, each disease is unique in its clinical presentation, histopathology, and immunofluorescence patterns, which allows for accurate diagnosis and disease-specific treatment strategy. Treatment of these disorders is complex and requires expert knowledge of disease pathogenesis. We review common treatment approaches for each of these disorders.

Introduction

The group of subepidermal immunobullous diseases encompasses many specific disorders including bullous pemphigoid (BP), linear IgA disease (LAD), dermatitis herpetiformis (DH), and epidermolysis bullosa acquisita (EBA), among others. As each of these diseases is characterized by an autoimmune response directed against skin adhesion molecules, there is a common thread to treatment approaches; however, each disease has clinical and immunological subtleties that further refine treatment strategy. As with many rare disorders, a standard approach to treatment is limited by lack of large randomized controlled trials. This review focuses on treatment of BP, LAD, DH, and EBA.

Bullous pemphigoid

BP is an autoimmune disorder characterized by autoan-tibodies directed against BP180 (collagen type XVII, BPAg2) and less often BP230 (BPAg1).[1–3] Recent studies have revealed that eventual blister formation is the result of multiple complex interactions involving autoantibody binding and complement activation leading to activation of cells such as neutrophils, eosinophils, and mast cells.[4–7] First-line treatments are typically general immunosuppressives, but newer agents that target these distinct steps in disease pathogenesis are beginning to emerge. Disease presentation may be limited to a localized form or may present with a widespread, generalized blistering eruption. As a result, treatment of BP depends greatly on the extent of disease as well as patient comorbidities. Interventions for the treatment of BP was the recent subject of a Cochrane review update, which provides a detailed summary of the most evidence-based approach to therapy.[8]

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Topical corticosteroids

Potent topical corticosteroids alone are often successful in treating limited or localized BP.[9–12] More recent studies have suggested that high-potency topical steroids are also useful in treating more severe disease. A 1992 report revealed that high doses of superpotent topical corticosteroids at 40 g/d were more effective and increased survival in patients with moderate and severe BP compared with oral prednisone at 1 mg/kg/d in a large, controlled trial of 34 patients.[13] In this study, patients were treated with clobetasol propionate cream at 40 g/d with a slow taper over 12 months. Several patients experienced local and systemic complications, possibly because of the high dose and length of treatment. To this end, a follow-up multicenter randomized controlled trial of 312 patients was designed to test whether a milder regimen of topical corticosteroids could achieve the same level of disease control with decreased side effects. Results showed that the mild regimen of topical corticosteroids (clobetasol propionate cream 10 to 30 g/d with a 4-month taper) was equally as effective as the previous dosing regimen.[14] In addition, for patients with moderate disease, those treated with the mild regimen showed a twofold decrease in the risk of death or life-threatening adverse events compared with the standard dosing. Many have argued that the efficacy of high-potency topical steroids is simply a result of systemic absorption. For example, a 30-g/d application of clobetasol propionate cream results in absorption of a dose of steroid equivalent to 45 mg/d of oral prednisone.[15] Such widespread topical therapy can be expensive and difficult to apply, particularly for the elderly, which often proves prohibitive in many patients. In our experience, the use of high-potency topical steroids has been useful in controlling the localized forms of BP. It appears that the use of high-potency topical steroids to treat BP patients with widespread skin disease is not a common practice among US dermatologists treating these patients (Luis A. Diaz, unpublished observation, 2011).

Although not a corticosteroid, tacrolimus is the only other topical agent reported to be useful in treating BP. These reports, however, are limited and involve a small number of cases of localized BP.[10,16–19]

Systemic corticosteroids

More extensive disease is usually treated with oral prednisone, which is the mainstay of therapy.[10,20,21] Although none of the randomized, controlled trials performed to date has included a placebo arm, there are 2 studies evaluating systemic steroids as single-agent treatment.[22,23] Varying doses of prednisolone 0.75 mg/ kg/d (n = 24) versus 1.25 mg/kg/d (n = 22) were compared in a multicenter randomized trial with no significant difference in new blister formation or healing of existing lesions at days 21 and 51.[23] In the second study, 2 formulations of oral steroids were compared: prednisolone 1.16 mg/kg/d (n = 29) versus methylprednisolone 1.17 mg/ kg/d (n = 28).[22] At day 10 of treatment, both groups showed a large reduction in the number of bullous lesions, but there was no statistically significant difference between the groups. The authors reported a significant decrease in the intensity of pruritus that was more pronounced in the methylprednisolone group ($P < .05$), but no difference in the regression of erythema between the 2 treatment groups.[22] Finally, high-dose “pulse” therapy with intravenous methylprednisolone also has been reported to be effective in rapidly controlling active blister formation in hospitalized BP patients, although the study was limited by lack of a control group and small sample size (n = 8).[24]

Although the optimal dosing and formulation of systemic corticosteroid therapy remains unclear, the complications of such therapy (including osteoporosis, diabetes, hypertension, cataracts, glaucoma, and systemic infection) may be especially severe, particularly in the elderly[25]; therefore, it is important to minimize the total dose and duration of therapy with oral glucocorticoids. In our experience, as well as others,[26] a starting dose of prednisone of

0.75 to 1.00 mg/ kg/d or even less may be adequate to achieve disease control. Once the development of blisters has been arrested and the erythema has subsided, a careful tapering of the prednisone is recommended. This objective is usually reached by the end of second week of therapy, when the patient is already receiving an adjuvant immunosuppressive drug. A weekly lowering of 5 mg to reach 30 mg is commonly used. Tapering the steroids below 30 mg should be done gradually and slowly, following an alternate day scheme. In our experience, decreasing prednisone by 2.5 mg every week on alternate days is very rewarding and prevents relapses. Tapering of the dose must be done according to the clinical response of the patients. The addition of steroid-sparing agents, such as those listed in the following sections, may facilitate tapering of systemic corticosteroids and help to minimize corticosteroid-associated adverse events.

Azathioprine

Azathioprine is a prodrug that is converted in non-enzymatic fashion to 6-mercaptopurine (6-MP). 6-MP is subsequently converted into 6-tioguanine nucleotides, which function as nucleotide analogs and lead to eventual lymphocyte impairment. When added to prednisone, azathioprine may allow for a decrease in the dosing of corticosteroids. A pioneer study in 1978[27] showed that although there was no difference in level of disease control at 3 years between patients on prednisone plus azathioprine 2.5 mg/kg/d (n = 12) and those on prednisone alone (n = 13), the addition of azathioprine allowed for a 45% reduction in the amount of prednisone necessary to control disease during the 3-year treatment period ($P < .01$).

A subsequent study also failed to show any difference in disease control (defined as no new blister formation) at the 28-day and 6-month follow-up when azathioprine was added to prednisone treatment (prednisone alone 1 mg/kg/d, n = 31; prednisone 1 mg/kg/d plus azathioprine 100 to 150 mg/d, n = 36)[28]; however, the steroid-sparing ability of adding azathioprine was not reported as an outcome measure.

In both studies, there were no statistically significant differences in mortality between treatment groups.

The most significant adverse effect noted with the addition of azathioprine in these studies was a reduction in the white cell count. Myelosuppression is a known potential side effect of azathioprine. Risk of myelosuppresion while on azathioprine may be related to thiopurine methyltransferase (TPMT) activity, an enzyme that converts 6-MP into inactive metabolites. Patients with low (or absent) TPMT activity will have a compensatory increase in conversion of 6-MP to active metabolites, leading to increased susceptibility to treatment-related myelosuppression.[29,30] Preemptive testing of TPMT activity levels may allow for a more tailored dosing, such that patients with a low TPMT activity level are started on a lower initial dosing, thereby minimizing their risk of myelosuppression.[30,31] In addition, patients with a high TPMT activity level may require higher doses to see any appreciable effect from the addition of azathioprine.[30] As TPMT testing was not available at the time the studies on azathioprine described previously were conducted, suboptimal dosing may account for the lack of apparent effect. In our practice, we typically start patients at a dose of 50 mg/d and slowly titrate the dosing based on TPMT activity and weight.

Adverse effects other than myelosuppression include cytopenia, hepatitis, pancreatitis, and an increased risk of infection. Careful monitoring of patients on azathioprine is necessary to detect signs or symptoms that may indicate toxicity. Finally, there is the potential for serious drug interactions when azathioprine is given to patients taking certain medications. Allopurinol inhibits xanthine oxidase, thereby shunting 6-MP toward conversion to active metabolites and, thus, increasing the potential for myelosuppression.[32] Azathioprine has

been implicated in inducing warfarin resistance. As a result, warfarin doses may need to be increased when azathioprine is added.[33] A complete review of all concurrent medications is critical to avoiding serious drug interactions.

Mycophenolate mofetil

Mycophenolate mofetil (MMF) inhibits inosine monophosphate dehydrogenase, which controls the rate of synthesis of guanine monophosphate, in turn impairing purine synthesis and altering the function of proliferating T and B cells. MMF has been used to control transplant rejection. The use of MMF in BP has predominantly been limited to case reports and small case series with noted efficacy.[34–37] Some of these reports have even shown successful control of disease using MMF as monotherapy in select patients,[35,36] although it is typically added to systemic corticosteroids for potential steroid-sparing effect. More recently, a multicenter, randomized trial compared MMF 1 g twice daily (n = 35) and azathioprine 2 mg/kg/d (n = 38) as adjuvant therapy to oral methylprednisolone 0.5 mg/kg/d in 73 BP patients.[38] These medications showed similar efficacy in terms of time to complete remission (defined as complete reepithelialization of all lesions), cumulative dose of systemic steroids, and duration of remission. Although the efficacy of the 2 drugs was similar, the azathioprine plus methylprednisolone group had significantly higher toxicity grades for aspartate aminotransferase, alanine aminotransferase, and -glutamyltransferase, when compared with the MMF plus methylprednisolone group, all of which reached statistical significance.[38] One important point to note is that TPMT levels were not checked in the azathioprine group before treatment. No methylprednisolone-only arm was included in this study.

Side effects of MMF include risk of systemic infection, cytopenias, and more commonly, gastrointestinal symptoms such as nausea, vomiting, diarrhea, abdominal pain, and anal tenderness.[39] Hepatotoxicity may also occur. Some drugs may decrease the absorption of MMF, including cholestyramine (enterohepatic circulation) and magnesium or aluminum hydroxides. Acyclovir and ganciclovir can increase MMF levels by competing for renal tubular excretion.[39]

Cyclophosphamide

Cyclophosphamide is a nitrogen mustard alkylating agent that is metabolized in the liver to active forms of the drug. These active metabolites are known to attach alkyl groups to guanine and crosslink DNA, leading to cell death. Cyclophosphamide has been used to treat patients with a variety of cancers and autoimmune diseases including pemphigus vulgaris and BP. Although cyclophosphamide is often used to treat ocular cicatricial pemphigoid, several case reports have suggested that cyclophosphamide may also be useful in cases of severe or refractory BP when given in either oral daily (1–5 mg/kg/d) or pulse intravenous dosing.[40,41] No large or randomized trials have been performed using this medication.

Side effects can be severe and include infection, nausea, vomiting, leucopenia, thrombocytopenia, increased risk of lymphoma, and hemorrhagic cystitis, which occurs in 40% of patients.[39] Hemorrhagic cystitis is attributable to the toxic metabolite acrolein and is associated with an increased risk of transitional cell carcinoma of the bladder. Mesna (sodium 2-mercaptoethanesulfonate) is a scavenging agent that binds acrolein and may be used to prevent hemorrhagic cystitis. Increased fluid intake and frequent voiding are also recommended to decrease bladder toxicity.[39]

Methotrexate

Methotrexate (MTX) inhibits the reduction of folic acid by the enzyme dehydrofolate reductase, leading to depletion of nucleotide precursors, which in turn impairs the synthesis

of DNA, RNA, and proteins. As an antimetabolite, immunosuppressive agent, and anti-inflammatory drug, MTX is used in the treatment of cancer and autoimmune disease. Although no randomized, controlled trials have been performed, there are several reports of low-dose weekly MTX being effective in combination with oral or topical corticosteroids. There is a report of a series of 11 consecutive patients with BP who were not responding to potent topical steroids.[42] MTX was started at 5 mg/wk and increased by 2.5 mg/wk to a maximum of 12.5 mg/wk. All patients responded with a decrease in disease activity and in 8 of 11 patients, the disease was controlled with minimal doses of MTX (5.0 to 7.5 mg/wk), whereas 3 of 11 required higher doses (10–12.5 mg/wk).[42] Other studies have corroborated these findings.[43] Similar results were obtained when comparable doses of MTX were administered via intramuscular injection.[44] A recent meta-analysis included results of 6 studies of MTX used in a total of 79 BP patients.[45] Overall, 94% of BP patients showed clinical improvement on MTX. Finally, a single-center retrospective analysis of 98 patients on MTX for BP showed a decrease in the time to complete remission compared with those on prednisone alone.[46] Many of these patients were controlled with MTX as monotherapy.[46] Although there have been no randomized, controlled trials of MTX in BP, the above findings are certainly promising and warrant further investigation.

Side effects of MTX are well known and include pancytopenia and hepatotoxicity.[39,43,46] Patients with renal disease, those on nonsteroidal anti-inflammatories, and those with no folic acid supplementation are at increased risk of pancytopenia. Folinic acid (Leucovorin) can be given as a rescue for myelosuppression if needed. Hepatic fibrosis and cirrhosis can occur with chronic administration. Patients with liver compromise (hepatitis B or C, alcohol use, diabetes, and obesity) are at increased risk of liver complications.[39,43,46] Photosensitivity and radiation recall are known complications of MTX therapy. The most common side effects include fatigue, nausea, and vomiting, which can often be overcome with folic acid supplementation.[39,43,46] MTX is known to have numerous drug interactions. Nonsteroidal anti-inflammatories, salicylates, and sulfonamides (trimethoprim-sulfamethoxazole, dapsone) displace MTX from plasma proteins and decrease renal excretion, thereby increasing MTX levels. Chloramphenicol, phenothiazines, phenytoin, and tetracyclines also increase MTX levels by displacement from plasma proteins. It is prudent to monitor liver function and complete blood counts in patients on this medication. Liver ultrasound and/or biopsy may be considered following 1.5 g of cumulative dose.[39,43,46]

Dapsone

Dapsone is a drug with chemotherapeutic and anti-infectious properties. Its utility in the treatment of skin disorders, particularly those involving neutrophil dysfunction, is well known.[47–49] A recent meta-analysis reviewed data from 6 studies with a total of 170 BP patients.[50] Dapsone was used alone or in combination with corticosteroids and/or other immunosuppressive therapy. Altogether, 81% of patients showed clinical improvement on dapsone at doses ranging from 50 to 300 mg/d.[50] Dapsone was more useful in combination with steroids or other immunosuppressives than as monotherapy. Hemolysis was the most common adverse event and was dose related in these studies.

Other potential side effects from dapsone include methemoglobinemia, hemolysis, idiopathic agranulocytosis, and anemia. Methemoglobinemia occurs in almost all patients but is clinically significant when methemoglobin levels reach 30% or higher.[51] Symptoms of dyspnea, nausea, and tachycardia may be early signs of toxicity. Hemolysis is also a predictable side effect in patients on dapsone.[52] It occurs in a dose-dependent manner and is reversible to some extent. Glucose-6-phosphate dehydrogenase level should be checked before starting dapsone, as deficiency of this enzyme increases the risk of hemolysis. Addition of cimetidine may reduce the anemia associated with dapsone.[53] A more rare and serious side effect is dapsone hypersensitivity syndrome, which presents with fever,

lymphadenopathy, and dermatitis.[54] Peripheral neuropathy involving motor neurons of extremities can also complicate treatment with dapsone at doses greater than 100 mg/d. It is typically reversible within 1 year of discontinuation of dapsone.[53]

Antimicrobials

Reports have described successful treatment of some BP patients with tetracycline and nicotinamide or variations on this theme, such as erythromycin and nicotinamide or tetracycline alone.[55–57] The authors have not had success with this treatment.

Plasmapheresis

As BP is mediated in large part by autoantibodies, several therapies are aimed at their elimination. Plasmapheresis (and plasma exchange) involves removal of large amounts of patient plasma over the course of several days and is typically performed during a hospitalization, given the risk for fluid overload during the fluid/protein replacement phase. Early studies have shown that the addition of plasma exchange to prednisolone reduced the amount of prednisolone (both daily and cumulative dose) necessary to achieve disease control (defined as lack of new blister formation and resolution of old lesions) at 1-month follow-up.[58] The steroid-sparing effect of plasmapheresis was corroborated in 2 studies[59,60]; however, a third study failed to show any benefit when plasma exchange was added to prednisolone.[28] Given its cost and associated risk, plasmapheresis is best reserved for patients with recalcitrant disease that does not respond to more standard therapy.

Intravenous immunoglobulin

Intravenous immunoglobulin (IVIg) has been used to reduce circulating autoantibodies in many autoimmune disorders, including pemphigus.[61] Although the exact mechanism of action is not completely clear, IVIg may act by increasing antibody catabolism.[62] Use of IVIg in patients with BP has been limited to case reports and series with conflicting results[63–66]; however, a recent meta-analysis of 17 cases showed that 70% of patients experienced a beneficial clinical response to IVIg.[67] The largest case series to date describes 15 patients with recurrent BP who experienced significant side effects from more conventional therapy.[68] In these patients, IVIg at a dose of 2 g/kg/cycle resulted in clinical remission in all patients and showed a steroid-sparing effect. There were no serious side effects. Potential side effects of IVIg are numerous and include anaphylaxis, infection, thrombosis, and renal failure.[69] In addition, this therapy is quite expensive. These factors should limit its use to patients with severe, refractory disease or severe complications on conventional therapy.

Rituximab

Rituximab is a monoclonal antibody directed against the B lymphocyte cell-surface protein CD20. Rituximab is becoming increasingly used for refractory pemphigus; however, use in BP is limited.[70] Initial reports describe complete remission in 2 cases of BP in patients receiving rituximab for chronic lymphocytic leukemia.[71] Following these initial observations, an increasing number of case reports emerged reporting mixed results when rituximab is used in BP.[72–77] A recent summary of the literature revealed that 7 of 9 BP patients treated with rituximab showed complete remission, whereas 2 of 2 patients showed at least partial remission. To these existing reports, an additional 5 cases were added, in which 3 patients experienced complete remission, 1 partial remission, and 1 patient died.[73]

Omalizumab

As the role of IgE in the pathogenesis of BP emerges, focus has turned to promising new drugs, such as omalizumab, a monoclonal antibody that prevents binding of IgE to the high-

affinity Fc*ε*RI. There is a single case of steroid-unresponsive BP with clinical improvement following 16 weeks of omalizumab treatment.[78] Although the patient experienced clinical improvement within 1 week of her first dose, she did have residual disease at the end of the 16-week trial. An open-label, randomized trial of omalizumab for BP is currently under way, and highlights how advances in understanding the pathogenesis of BP may translate directly to new therapeutic targets.

Linear IgA disease

LAD is a subepidermal blistering disorder characterized clinically by tense bullae, often in a "crown of jewels" configuration.[79] Histologically, LAD shows a subepidermal split with linear IgA staining on direct immunofluorescence. Although clinical trials are lacking, the treatment of choice is dapsone with or without systemic corticosteroids.[80,81] For a review of dosing, side effects, and monitoring of dapsone, please refer to the previous section, which describes the use of dapsone in the treatment of BP. Other reported treatments include colchicine,[82–86] trimethoprin-sulfamethoxazole,[87] tacrolimus ointment,[88] mycophenolate,[89] immunoadsorption,[90] and IVIg.[91,92] Obviously, in drug-induced cases, the offending medication should be discontinued.

Treatment protocols used by the authors for BP and LAD patients

The aim of the therapy is to arrest the cutaneous inflammatory syndrome triggered by the autoimmune process mediated by autoantibodies against the hemidesmosomal BP180 antigen.

Patients with localized disease

For patients with localized disease, treatment with high-potency topical steroids (clobetasol) and wet dressings with physiologic saline are preferred.

Patients with widespread disease

For patients with widespread disease, treatment with systemic steroids (prednisone, 60 to 80 mg/d) along with a steroid-sparing agent is preferred. We start with azathioprine or MTX in a large number of patients. The weekly doses of MTX may be effective and very appealing to some patients. Other patients may respond well to mycophenolate mofetyl using doses stated previously. In patients with contraindications to these drugs, dapsone or cyclophosphamide may be used. Only in rare patients have we used IVIg or plasmapheresis. Slow tapering of the steroids is crucial in preventing relapses.

Dermatitis herpetiformis

DH is a cutaneous manifestation of gluten sensitivity.[93] Clinically, it is characterized by small blisters over extensor surfaces and histologically by collections of neutrophils in the dermal papillae with subepidermal blister formation. Immunofluorescence findings of granular IgA deposits in the dermal papillae are confirmatory. The first-line medical treatment is dapsone, which often leads to clinical improvement within days of starting the medication.[94–97] Dapsone should be started at 25 to 50 mg/d and slowly increased to 100 to 200 mg/d based on clinical response and medication tolerance. Monitoring for potential side effects is critical given the risk of hemolytic anemia, methemoglobinemia, neuropathy, and hypersensitivity (discussed in more detail previously in the section describing the use of dapsone in the treatment of BP). Sulfasalazine and sulfamethoxypyridazine can be useful in patients who cannot tolerate dapsone or when dapsone is ineffective[98,99]; however, the mainstay of therapy is initiation of a gluten-free diet, as this reduces the need for medication, resolves underlying enteropathy, and reduces the risk of lymphoma in these patients.[100]

Patients should be referred to a dietician for guidance on adhering to a gluten-free diet, as many food ingredients contain gluten. There are also published lists of foods that contain gluten that may be helpful to patients.[101]

Epidermolysis bullosa acquisita

EBA is an acquired blistering disorder with autoantibodies predominantly against collagen VII. Noninflammatory blisters typically occur at sites of trauma, although the clinical presentation can be varied with more widespread inflammatory blisters in some patients. The areas heal with scarring and milia.[102] Histologic study shows subepidermal blister formation and direct immunofluorescence shows linear IgG along the basement membrane zone. No randomized, controlled trials have been performed to date, but several case reports and series have been published.[103] There is no clear first-line treatment for EBA, as all therapies tend to be only partially effective as reported in a summary of the literature.[104] Colchicine has been reported to be effective in some patients at high doses, although side effects, such as diarrhea, often limit dose escalation and not all patients show improvement.[105–107] There are several case reports of IVIg improving blister formation in EBA alone or in combination with other agents.[65,104,108] Other immunomodulatory agents (cyclosporine, dapsone, azathioprine) have been effective in reducing blister formation and corticosteroid dose some patients.[104,109–111] Systemic steroids, which are useful in so many autoimmune bullous disorders, do not appear to be as effective in EBA, particularly when used as monotherapy in the noninflammatory immunobullous form of EBA.[104,110,112]

Conclusions

Treatment of subepidermal immunobullous disorders is complex and requires knowledge of the clinical, histological, and immunological features of each particular disease. As most medications used to treat these disorders carry a high risk of side effects, any treatment plan should be initiated only after consideration of patient comorbidities, concurrent medications, extent of disease, and impact of the disease on quality of life. Treatment changes should be guided by patient response, tolerance of medication, and, occasionally, immunological parameters. Close follow-up and monitoring for medication side effects is critical for successful treatment of these complex disorders.

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References

1. Beutner EH, Lever WF, Witebsky E, et al. Autoantibodies in pemphigus vulgaris: response to an intercellular substance of epidermis. JAMA. 1965; 192:682–8. [PubMed: 14280515]
2. Jordon RE, Beutner EH, Witebsky E, et al. Basement zone antibodies in bullous pemphigoid. JAMA. 1967; 200:751–6. [PubMed: 4164640]
3. Lever WF. Pemphigus. Medicine (Baltimore). 1953; 32:1–123. [PubMed: 13024494]
4. Liu Z, Giudice GJ, Swartz SJ, et al. The role of complement in experimental bullous pemphigoid. J Clin Invest. 1995; 95:1539–44. [PubMed: 7706459]
5. Liu Z, Giudice GJ, Zhou X, et al. A major role for neutrophils in experimental bullous pemphigoid. J Clin Invest. 1997; 100:1256–63. [PubMed: 9276744]
6. Woodley DT. The role of IgE anti-basement membrane zone autoantibodies in bullous pemphigoid. Arch Dermatol. 2007; 143:249–50. [PubMed: 17310005]
7. Zone JJ, Taylor T, Hull C, et al. IgE basement membrane zone antibodies induce eosinophil infiltration and histological blisters in engrafted human skin on SCID mice. J Invest Dermatol. 2007; 127:1167–74. [PubMed: 17235329]

8. Kirtschig G, Middleton P, Bennett C, et al. Interventions for bullous pemphigoid. Cochrane Database Syst Rev. 2010:CD002292. [PubMed: 20927731]
9. Ahmed AR, Maize JC, Provost TT. Bullous pemphigoid. Clinical and immunologic follow-up after successful therapy. Arch Dermatol. 1977; 113:1043–6. [PubMed: 329769]
10. Fine JD. Management of acquired bullous skin diseases. N Engl J Med. 1995; 333:1475–84. [PubMed: 7477149]
11. Hadi SM, Barnetson RS, Gawkrodger DJ, et al. Clinical, histological and immunological studies in 50 patients with bullous pemphigoid. Dermatologica. 1988; 176:6–17. [PubMed: 3276569]
12. Westerhof W. Treatment of bullous pemphigoid with topical clobetasol propionate. J Am Acad Dermatol. 1989; 20:458–61. [PubMed: 2645323]
13. Joly P, Roujeau JC, Benichou J, et al. A comparison of oral and topical corticosteroids in patients with bullous pemphigoid. N Engl J Med. 2002; 346:321–7. [PubMed: 11821508]
14. Joly P, Roujeau JC, Benichou J, et al. A comparison of two regimens of topical corticosteroids in the treatment of patients with bullous pemphigoid: a multicenter randomized study. J Invest Dermatol. 2009; 129:1681–7. [PubMed: 19177141]
15. Bystryn JC, Wainwright BD, Shupack JL. Oral and topical corticosteroids in bullous pemphigoid. N Engl J Med. 2002; 347:143–5. author reply 145. [PubMed: 12117001]
16. Chu J, Bradley M, Marinkovich MP. Topical tacrolimus is a useful adjunctive therapy for bullous pemphigoid. Arch Dermatol. 2003; 139:813–5. [PubMed: 12810523]
17. Chuh AA. The application of topical tacrolimus in vesicular pemphigoid. Br J Dermatol. 2004; 150:622–3. [PubMed: 15030368]
18. Ko MJ, Chu CY. Topical tacrolimus therapy for localized bullous pemphigoid. Br J Dermatol. 2003; 149:1079–81. [PubMed: 14632824]
19. Lebeau S, Mainetti C, Masouye I, et al. Localized childhood vulval pemphigoid treated with tacrolimus ointment. Dermatology. 2004; 208:273–5. [PubMed: 15118388]
20. Patton T, Korman NJ. Bullous pemphigoid treatment review. Expert Opin Pharmacother. 2006; 7:2403–11. [PubMed: 17109614]
21. Wojnarowska F, Kirtschig G, Highet AS, et al. Guidelines for the management of bullous pemphigoid. Br J Dermatol. 2002; 147:214–21. [PubMed: 12174090]
22. Dreno B, Sassolas B, Lacour P, et al. Methylprednisolone versus prednisolone methylsulfobenzoate in pemphigoid: a comparative multicenter study. Ann Dermatol Venereol. 1993; 120:518–21. [PubMed: 8304707]
23. Morel P, Guillaume JC. Treatment of bullous pemphigoid with prednisolone only: 0.75 mg/kg/day versus 1.25 mg/kg/day A multicenter randomized study. Ann Dermatol Venereol. 1984; 111:925–8. [PubMed: 6395773]
24. Siegel J, Eaglstein WH. High-dose methylprednisolone in the treatment of bullous pemphigoid. Arch Dermatol. 1984; 120:1157–65. [PubMed: 6383221]
25. Savin JA. The events leading to the death of patients with pemphigus and pemphigoid. Br J Dermatol. 1979; 101:521–34. [PubMed: 391261]
26. Khumalo NP, Murrell DF, Wojnarowska F, et al. A systematic review of treatments for bullous pemphigoid. Arch Dermatol. 2002; 138:385–9. [PubMed: 11902990]
27. Burton JL, Harman RR, Peachey RD, et al. Azathioprine plus prednisone in treatment of pemphigoid. Br Med J. 1978; 2:1190–1. [PubMed: 363229]
28. Guillaume JC, Vaillant L, Bernard P, et al. Controlled trial of azathioprine and plasma exchange in addition to prednisolone in the treatment of bullous pemphigoid. Arch Dermatol. 1993; 129:49–53. [PubMed: 8420491]
29. Collie-Duguid ES, Pritchard SC, Powrie RH, et al. The frequency and distribution of thiopurine methyltransferase alleles in Caucasian and Asian populations. Pharmacogenetics. 1999; 9:37–42. [PubMed: 10208641]
30. Snow JL, Gibson LE. The role of genetic variation in thiopurine methyltransferase activity and the efficacy and/or side effects of azathioprine therapy in dermatologic patients. Arch Dermatol. 1995; 131:193–7. [PubMed: 7857117]

31. Tavadia SM, Mydlarski PR, Reis MD, et al. Screening for azathioprine toxicity: a pharmacoeconomic analysis based on a target case. J Am Acad Dermatol. 2000; 42:628–32. [PubMed: 10727309]
32. Cummins D, Sekar M, Halil O, et al. Myelosuppression associated with azathioprine-allopurinol interaction after heart and lung transplantation. Transplantation. 1996; 61:1661–2. [PubMed: 8669118]
33. Vazquez SR, Rondina MT, Pendleton RC. Azathioprine-induced warfarin resistance. Ann Pharmacother. 2008; 42:1118–23. [PubMed: 18505911]
34. Bohm M, Beissert S, Schwarz T, et al. Bullous pemphigoid treated with mycophenolate mofetil. Lancet. 1997; 349:541. [PubMed: 9048797]
35. Grundmann-Kollmann M, Kaskel P, Leiter U, et al. Treatment of pemphigus vulgaris and bullous pemphigoid with mycophenolate mofetil monotherapy. Arch Dermatol. 1999; 135:724–5. [PubMed: 10376713]
36. Grundmann-Kollmann M, Korting HC, Behrens S, et al. Mycophenolate mofetil: a new therapeutic option in the treatment of blistering autoimmune diseases. J Am Acad Dermatol. 1999; 40:957–60. [PubMed: 10365927]
37. Nousari HC, Griffin WA, Anhalt GJ. Successful therapy for bullous pemphigoid with mycophenolate mofetil. J Am Acad Dermatol. 1998; 39:497–8. [PubMed: 9738791]
38. Beissert S, Werfel T, Frieling U, et al. A comparison of oral methylprednisolone plus azathioprine or mycophenolate mofetil for the treatment of bullous pemphigoid. Arch Dermatol. 2007; 143:1536–42. [PubMed: 18087004]
39. Kasperkiewicz M, Schmidt E. Current treatment of autoimmune blistering diseases. Curr Drug Discov Technol. 2009; 6:270–80. [PubMed: 20025595]
40. Dawe RS, Naidoo DK, Ferguson J. Severe bullous pemphigoid responsive to pulsed intravenous dexamethasone and oral cyclophosphamide. Br J Dermatol. 1997; 137:826–7. [PubMed: 9415254]
41. Itoh T, Hosokawa H, Shirai Y, et al. Successful treatment of bullous pemphigoid with pulsed intravenous cyclophosphamide. Br J Dermatol. 1996; 134:931–3. [PubMed: 8736339]
42. Heilborn JD, Stahle-Backdahl M, Albertioni F, et al. Low-dose oral pulse methotrexate as monotherapy in elderly patients with bullous pemphigoid. J Am Acad Dermatol. 1999; 40:741–9. [PubMed: 10321603]
43. Bara C, Maillard H, Briand N, et al. Methotrexate for bullous pemphigoid: preliminary study. Arch Dermatol. 2003; 139:1506–7. [PubMed: 14623719]
44. Dereure O, Bessis D, Guillot B, et al. Treatment of bullous pemphigoid by low-dose methotrexate associated with short-term potent topical steroids: an open prospective study of 18 cases. Arch Dermatol. 2002; 138:1255–6. [PubMed: 12225001]
45. Gurcan HM, Ahmed AR. Analysis of current data on the use of methotrexate in the treatment of pemphigus and pemphigoid. Br J Dermatol. 2009; 161:723–31. [PubMed: 19548961]
46. Kjellman P, Eriksson H, Berg P. A retrospective analysis of patients with bullous pemphigoid treated with methotrexate. Arch Dermatol. 2008; 144:612–6. [PubMed: 18490587]
47. Booth SA, Moody CE, Dahl MV, et al. Dapsone suppresses integrin-mediated neutrophil adherence function. J Invest Dermatol. 1992; 98:135–40. [PubMed: 1732379]
48. Debol SM, Herron MJ, Nelson RD. Anti-inflammatory action of dapsone: inhibition of neutrophil adherence is associated with inhibition of chemoattractant-induced signal transduction. J Leukoc Biol. 1997; 62:827–36. [PubMed: 9400824]
49. Harvath L, Yancey KB, Katz SI. Selective inhibition of human neutrophil chemotaxis to N-formyl-methionyl-leucyl-phenylalanine by sulfones. J Immunol. 1986; 137:1305–11. [PubMed: 3016092]
50. Gurcan HM, Ahmed AR. Efficacy of dapsone in the treatment of pemphigus and pemphigoid: analysis of current data. Am J Clin Dermatol. 2009; 10:383–96. [PubMed: 19824739]
51. Wolf R, Matz H, Orion E, et al. Dapsone. Dermatol Online J. 2002; 8:2. [PubMed: 12165212]
52. Coleman MD. Dapsone: modes of action, toxicity and possible strategies for increasing patient tolerance. Br J Dermatol. 1993; 129:507–13. [PubMed: 8251346]
53. Rhodes LE, Coleman MD, Lewis-Jones MS. Dapsone-induced motor peripheral neuropathy in pemphigus foliaceus. Clin Exp Dermatol. 1995; 20:155–6. [PubMed: 8565254]

54. Zhu YI, Stiller MJ. Dapsone and sulfones in dermatology: overview and update. J Am Acad Dermatol. 2001; 45:420–34. [PubMed: 11511841]
55. Berk MA, Lorincz AL. The treatment of bullous pemphigoid with tetracycline and niacinamide. A preliminary report. Arch Dermatol. 1986; 122:670–4. [PubMed: 2940979]
56. Fivenson DP, Breneman DL, Rosen GB, et al. Nicotinamide and tetracycline therapy of bullous pemphigoid. Arch Dermatol. 1994; 130:753–8. [PubMed: 8002646]
57. Kolbach DN, Remme JJ, Bos WH, et al. Bullous pemphigoid successfully controlled by tetracycline and nicotinamide. Br J Dermatol. 1995; 133:88–90. [PubMed: 7669647]
58. Roujeau JC, Guillaume JC, Morel P, et al. Plasma exchange in bullous pemphigoid. Lancet. 1984; 2:486–8. [PubMed: 6147549]
59. Egan CA, Meadows KP, Zone JJ. Plasmapheresis as a steroid saving procedure in bullous pemphigoid. Int J Dermatol. 2000; 39:230–5. [PubMed: 10759969]
60. Mazzi G, Raineri A, Zanolli FA, et al. Plasmapheresis therapy in pemphigus vulgaris and bullous pemphigoid. Transfus Apher Sci. 2003; 28:13–8. [PubMed: 12620264]
61. Ruetter A, Luger TA. Efficacy and safety of intravenous immunoglobulin for immune-mediated skin disease: current view. Am J Clin Dermatol. 2004; 5:153–60. [PubMed: 15186194]
62. Yu Z, Lennon VA. Mechanism of intravenous immune globulin therapy in antibody-mediated autoimmune diseases. N Engl J Med. 1999; 340:227–8. [PubMed: 9895405]
63. Beckers RC, Brand A, Vermeer BJ, et al. Adjuvant high-dose intravenous gammaglobulin in the treatment of pemphigus and bullous pemphigoid: experience in six patients. Br J Dermatol. 1995; 133:289–93. [PubMed: 7547400]
64. Godard W, Roujeau JC, Guillot B, et al. Bullous pemphigoid and intravenous gammaglobulin. Ann Intern Med. 1985; 103:964–5. [PubMed: 2415032]
65. Harman KE, Black MM. High-dose intravenous immune globulin for the treatment of autoimmune blistering diseases: an evaluation of its use in 14 cases. Br J Dermatol. 1999; 140:865–74. [PubMed: 10354024]
66. Tappeiner G, Steiner A. High-dosage intravenous gamma globulin: therapeutic failure in pemphigus and pemphigoid. J Am Acad Dermatol. 1989; 20:684–5. [PubMed: 2469705]
67. Engineer L, Ahmed AR. Role of intravenous immunoglobulin in the treatment of bullous pemphigoid: analysis of current data. J Am Acad Dermatol. 2001; 44:83–8. [PubMed: 11148470]
68. Ahmed AR. Intravenous immunoglobulin therapy for patients with bullous pemphigoid unresponsive to conventional immunosuppressive treatment. J Am Acad Dermatol. 2001; 45:825–35. [PubMed: 11712025]
69. Ahmed AR, Dahl MV. Consensus statement on the use of intravenous immunoglobulin therapy in the treatment of autoimmune mucocutaneous blistering diseases. Arch Dermatol. 2003; 139:1051–9. [PubMed: 12925395]
70. Joly P, D'Incan M, Musette P. Rituximab for pemphigus vulgaris. N Engl J Med. 2007; 356:521. author reply 522. [PubMed: 17267915]
71. Saouli Z, Papadopoulos A, Kaiafa G, et al. A new approach on bullous pemphigoid therapy. Ann Oncol. 2008; 19:825–6. [PubMed: 18325915]
72. Hertl M, Zillikens D, Borradori L, et al. Recommendations for the use of rituximab (anti-CD20 antibody) in the treatment of autoimmune bullous skin diseases. J Dtsch Dermatol Ges. 2008; 6:366–73. [PubMed: 18201220]
73. Lourari S, Herve C, Doffoel-Hantz V, et al. Bullous and mucous membrane pemphigoid show a mixed response to rituximab: experience in seven patients. J Eur Acad Dermatol Venereol.
74. Peterson JD, Chan LS. Effectiveness and side effects of anti-CD20 therapy for autoantibody-mediated blistering skin diseases: A comprehensive survey of 71 consecutive patients from the initial use to 2007. Ther Clin Risk Manag. 2009; 5:1–7. [PubMed: 19436603]
75. Schmidt E, Brocker EB, Goebeler M. Rituximab in treatment-resistant autoimmune blistering skin disorders. Clin Rev Allergy Immunol. 2008; 34:56–64. [PubMed: 18270859]
76. Schmidt E, Seitz CS, Benoit S, et al. Rituximab in autoimmune bullous diseases: mixed responses and adverse effects. Br J Dermatol. 2007; 156:352–6. [PubMed: 17223877]

77. Schulze J, Bader P, Henke U, et al. Severe bullous pemphigoid in an infant—successful treatment with rituximab. Pediatr Dermatol. 2008; 25:462–5. [PubMed: 18789089]

78. Fairley JA, Burnett CT, Fu CL, et al. A pathogenic role for IgE in autoimmunity: bullous pemphigoid IgE reproduces the early phase of lesion development in human skin grafted to nu/nu mice. J Invest Dermatol. 2007; 127:2605–11. [PubMed: 17611576]

79. Egan CA, Zone JJ. Linear IgA bullous dermatosis. Int J Dermatol. 1999; 38:818–27. [PubMed: 10583613]

80. Wojnarowska F, Kirtschig G, Khumalo N. Treatment of subepidermal immunobullous diseases. Clin Dermatol. 2001; 19:768–77. [PubMed: 11705687]

81. Aboobaker J, Wojnarowska FT, Bhogal B, et al. Chronic bullous dermatosis of childhood—clinical and immunological features seen in African patients. Clin Exp Dermatol. 1991; 16:160–4. [PubMed: 1934564]

82. Hernandez-Machin B, Penate Y, Baez B, et al. Linear IgA bullous dermatosis of adults treated with colchicine. Actas Dermosifiliogr. 2006; 97:549–50. [PubMed: 17067539]

83. Ang P, Tay YK. Treatment of linear IgA bullous dermatosis of childhood with colchicine. Pediatr Dermatol. 1999; 16:50–2. [PubMed: 10028001]

84. Aram H. Linear IgA bullous dermatosis. Successful treatment with colchicine. Arch Dermatol. 1984; 120:960–1. [PubMed: 6375580]

85. Banodkar DD, al-Suwaid AR. Colchicine as a novel therapeutic agent in chronic bullous dermatosis of childhood. Int J Dermatol. 1997; 36:213–6. [PubMed: 9159009]

86. Zeharia A, Hodak E, Mukamel M, et al. Successful treatment of chronic bullous dermatosis of childhood with colchicine. J Am Acad Dermatol. 1994; 30:660–1. [PubMed: 8157799]

87. Peterson JD, Chan LS. Linear IgA bullous dermatosis responsive to trimethoprim-sulfamethoxazole. Clin Exp Dermatol. 2007; 32:756–8. [PubMed: 17868394]

88. Dauendorffer JN, Mahe E, Saiag P. Tacrolimus ointment, an interesting adjunctive therapy for childhood linear IgA bullous dermatosis. J Eur Acad Dermatol Venereol. 2008; 22:364–5. [PubMed: 18269605]

89. Marzano AV, Ramoni S, Spinelli D, et al. Refractory linear IgA bullous dermatosis successfully treated with mycophenolate sodium. J Dermatolog Treat. 2008; 19:364–7. [PubMed: 19016105]

90. Kasperkiewicz M, Meier M, Zillikens D, et al. Linear IgA disease: successful application of immunoadsorption and review of the literature. Dermatology. 2010; 220:259–63. [PubMed: 20130384]

91. Segura S, Iranzo P, Martinez-de Pablo I, et al. High-dose intravenous immunoglobulins for the treatment of autoimmune mucocutaneous blistering diseases: evaluation of its use in 19 cases. J Am Acad Dermatol. 2007; 56:960–7. [PubMed: 17368865]

92. Khan IU, Bhol KC, Ahmed AR. Linear IgA bullous dermatosis in a patient with chronic renal failure: response to intravenous immunoglobulin therapy. J Am Acad Dermatol. 1999; 40:485–8. [PubMed: 10071325]

93. Caproni M, Antiga E, Melani L, et al. Guidelines for the diagnosis and treatment of dermatitis herpetiformis. J Eur Acad Dermatol Venereol. 2009; 23:633–8. [PubMed: 19470076]

94. Damodar S, Viswabandya A, George B, et al. Dapsone for chronic idiopathic thrombocytopenic purpura in children and adults—a report on 90 patients. Eur J Haematol. 2005; 75:328–31. [PubMed: 16146539]

95. Lee I, Barton TD, Goral S, et al. Complications related to dapsone use for pneumocystis jirovecii pneumonia prophylaxis in solid organ transplant recipients. Am J Transplant. 2005; 5:2791–5. [PubMed: 16212642]

96. Sener O, Doganci L, Safali M, et al. Severe dapsone hypersensitivity syndrome. J Investig Allergol Clin Immunol. 2006; 16:268–70.

97. Talarico JF, Metro DG. Presentation of dapsone-induced methemo-globinemia in a patient status post small bowel transplant. J Clin Anesth. 2005; 17:568–70. [PubMed: 16297761]

98. McFadden JP, Leonard JN, Powles AV, et al. Sulphamethoxypyridazine for dermatitis herpetiformis, linear IgA disease and cicatricial pemphigoid. Br J Dermatol. 1989; 121:759–62. [PubMed: 2692691]

99. Willsteed E, Lee M, Wong LC, et al. Sulfasalazine and dermatitis herpetiformis. Australas J Dermatol. 2005; 46:101–3. [PubMed: 15842404]
100. Garioch JJ, Lewis HM, Sargent SA, et al. 25 years' experience of a gluten-free diet in the treatment of dermatitis herpetiformis. Br J Dermatol. 1994; 131:541–5. [PubMed: 7947207]
101. Rottmann LH. Details of the gluten-free diet for the patient with dermatitis herpetiformis. Clin Dermatol. 1991; 9:409–14. [PubMed: 1806229]
102. Ishii N, Hamada T, Dainichi T, et al. Epidermolysis bullosa acquisita: what's new? J Dermatol. 37:220–30. [PubMed: 20507385]
103. Kirtschig G, Murrell D, Wojnarowska F, et al. Interventions for mucous membrane pemphigoid and epidermolysis bullosa acquisita. Cochrane Database Syst Rev. 2003:CD004056. [PubMed: 12535507]
104. Engineer L, Ahmed AR. Emerging treatment for epidermolysis bullosa acquisita. J Am Acad Dermatol. 2001; 44:818–28. [PubMed: 11312431]
105. Cunningham BB, Kirchmann TT, Woodley D. Colchicine for epidermolysis bullosa acquisita. J Am Acad Dermatol. 1996; 34:781–4. [PubMed: 8632074]
106. Megahed M, Scharffetter-Kochanek K. Epidermolysis bullosa acquisita—successful treatment with colchicine. Arch Dermatol Res. 1994; 286:35–46. [PubMed: 8141610]
107. Arora KP, Sachdeva B, Singh N, et al. Remission of recalcitrant epidermolysis bullosa acquisita (EBA) with colchicine monotherapy. J Dermatol. 2005; 32:114–9. [PubMed: 15906541]
108. Meier F, Sonnichsen K, Schaumburg-Lever G, et al. Epidermolysis bullosa acquisita: efficacy of high-dose intravenous immunoglobulins. J Am Acad Dermatol. 1993; 29:334–7. [PubMed: 8340508]
109. Gupta AK, Ellis CN, Nickoloff BJ, et al. Oral cyclosporine in the treatment of inflammatory and noninflammatory dermatoses. A clinical and immunopathologic analysis. Arch Dermatol. 1990; 126:339–50. [PubMed: 2178558]
110. Luke MC, Darling TN, Hsu R, et al. Mucosal morbidity in patients with epidermolysis bullosa acquisita. Arch Dermatol. 1999; 135:954–9. [PubMed: 10456345]
111. Clement M, Ratnesar P, Thirumoorthy T, et al. Epidermolysis bullosa acquisita—a case with upper airways obstruction requiring tracheostomy and responding to cyclosporin. Clin Exp Dermatol. 1993; 18:548–51. [PubMed: 8252795]
112. Woodley DT, Briggaman RA, Gammon WT. Review and update of epidermolysis bullosa fsacquisita. Semin Dermatol. 1988; 7:111–22. [PubMed: 3153432]