Chapter 8

Current Therapy in Autoimmune Bullous Diseases

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Additional information is available at the end of the chapter

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Abstract

The goal of the treatment of autoimmune bullous disease is to reduce the production of pathogenic autoantibodies or increase elimination of pathogenic autoantibodies from serum of the patients. Immunosuppressive therapy reduces the production of autoantibodies. The therapy protocol is divided into three phases. The first is a control phase with the highest dose of immunosuppressive drugs suppressing activity of disease, followed with a consolidation phase, when the bulk of lesions is healed. The last phase is a maintenance phase when immunosuppressive medication is gradually tapered to the lowest level that suppresses the appearance of new lesions. In complete remission off therapy, the patient reached complete clinical remission and does not use any immunosuppressive medication. In complete remission on therapy, the patient uses a minimal immunosuppressive therapy. The first-line treatment is corticosteroids in pemphigus and pemphigoid groups. Adjuvant immunosuppressive drugs are combined with systemic corticosteroids and display a corticosteroid sparing effect. First-line immunosuppressive adjuvants comprise azathioprine, mycophenolate mofetil and mycophenolic acid. Rituximab, intravenous immunoglobulin G, immunoadsorption, cyclophosphamide, dapsone, and methotrexate are regarded as the second-line adjuvants. In dermatitis herpetiformis, a gluten free diet eliminates the clinical symptoms. Dapsone is regarded to be a valid therapeutic option in management of dermatitis herpetiformis.

Keywords: immunosuppressive therapy, corticosteroids, azathioprine, mycophenolate mofetil, cyclophosphamide, methotrexate, dapsone, rituximab, intravenous immunoglobulin G, immunoadsorption, tetracycline, gluten free diet

1. Introduction

Autoimmune bullous diseases belong to disorders that have low incidence but a high morbidity and mortality. Rupturing of blisters leads to painful erosions that cause significant loss of body fluid, electrolytes and proteins, especially in cases with extensive body surface involvement. If

mucous membrane of the mouth, pharynx and esophagus are involved, the patient may not be able to tolerate adequate intake of food and medication. Erosions on the skin and mucosa can lead to secondary infections which may cause life-threatening events such as sepsis and cardiac failure. Autoimmune bullous diseases warrant the use of high dose of systemic corticosteroids and immunosuppressive drugs that may be associated with various adverse and other side effects. Moreover, considerable risk for serious systemic complications should be predicted.

Pemphigus vulgaris is a rare autoimmune bullous disease, but one of the most severe with the highest morbidity and mortality rates, and one requiring the highest doses of corticosteroids and adjuvant agents. Before the advent of systemic corticosteroids, the prognosis of pemphigus vulgaris was fatal within 2 years from diagnosis. The introduction of corticosteroids in the 1950s dramatically reduced mortality rates from around 70 to 30%. The use of adjuvant immunosuppressive agent in management of autoimmune bullous diseases in the 1960s decreases mortality rates to 10% [1]. Nowadays, it is estimated that mortality rates of pemphigus is in the range of 5–10% [2]. Among autoimmune bullous disease, the most frequent disorder is bullous pemphigoid. The mortality rate of bullous pemphigoid is age dependent and ranges in 2.43–9.5% [3]. A higher mortality is influenced by old age, widespread disease, high dose of oral corticosteroids and life-threatening comorbidities. Bullous pemphigoid has shown increasing incidence rates in recent decades, especially in Western societies. However, bullous pemphigoid rarely represents a life-threatening disease. In bullous pemphigoid, the risk factors that can evoke disease should be identified and eradicated. A provoking drug or underlying malignancy is the most frequent risk factors in bullous pemphigoid. In therapy management, many immunosuppressive drugs are contraindicated because of comorbidities or malignancy in the history.

The therapy modalities used to treat autoimmune bullous disease have different mechanisms affecting the pathophysiology of the disease. Some medications yield in suppression production of the pathogenic autoantibodies and some have anti-inflammatory activity. Immunosuppressive activity is used in the corticosteroids, azathioprine, mycophenolate mofetil, cyclophosphamide, methotrexate, and others. Medication with anti-inflammatory activity is aimed at suppressing the inflammatory process. The last group includes topical corticosteroids, dapsone and sulfonamides, as well as anti-inflammatory antibiotics. Immunoadsorption is another modality using the removal of the pathogenic autoantibodies and inflammatory mediators. A new biologic therapy is intravenous immunoglobulin G and rituximab, monoclonal antibody to transmembrane protein CD20 of B-cells. In general, immunosuppressive and anti-inflammatory medications are commonly utilized in various autoimmune bullous diseases. Dermatitis herpetiformis is one of the diseases with specific treatment regimen, namely a gluten free diet that may improve gluten reverses of underlying gluten-sensitive enteropathy and so the results in remission of the skin disease.

2. Management of autoimmune bullous diseases

Management of autoimmune bullous disease should start with initial evaluation of the disease and the patient's condition in order to evaluate the risk of complications developing from immunosuppressive therapy. The clinical diagnosis should be confirmed with the histopathology of the blister, direct immunofluorescence microscopy (DIF) of the perilesional skin,

serological detection of autoantibodies by indirect immunofluorescence microscopy (IIF), enzyme-linked immunosorbent assay (ELISA), or immunoblot or immunoprecipitation.

The work-up before corticosteroid or immunosuppressive therapy should account for: a complete blood count, creatinine, urea, blood electrolytes, transaminases, gamma GT, alkaline phosphatase, total serum protein, albumin, glucose, hepatitis B, C and HIV, and chest X-ray. Optional examination predicting used medication includes analysis of thiopurine methyltransferase (TPMT) activity when azathioprine is considered; glucose-6-phosphate dehydrogenase (G6PD) serum activity, bilirubin, and reticulocytes if dapsone is recommended; and serum IgA deficiency should be ruled out prior to intravenous immunoglobulin therapy. Abdominal sonography is optional. QuantiFERONE or PPD is recommended where there is a risk of tuberculosis; a βhuman chorionic gonadotropin (βHCG) blood test is used to exclude pregnancy in women of childbearing age; osteodensitometry is recommended prior to corticosteroid therapy and periodically evaluated during the regimen; ophthalmological examination is performed prior to corticosteroid therapy and periodically repeated to exclude glaucoma and cataract.

A general examination should asses the patient's general condition including bodyweight, arterial blood pressure, and comorbidities such as cardiovascular, musculoskeletal or neoplastic, diabetes, etc.

Laboratory monitoring of pathogenic autoantibodies should be performed in autoimmune bullous diseases to predict outcome of the disease as well as to evaluate the efficacy of the employed therapy regimen.

In pemphigus patients, detection of pathogenic IgG antibodies by ELISA is positive in 90% of patients and correlates with disease activity. A quantitative evaluation of anti-Dsg3 and anti-Dsg1 IgG is evaluated using ELISA or IIF. Both methods can predict activity or curability of disorder. Determination of serum antibodies is performed on initiation of therapy, after 3 months and every 3–6 months based on disease activity and relapse [4]. Immunoblot and immunoprecipitation can also be used. In paraneoplastic pemphigus, the autoantibody to various antigens can be detected, including envoplakin, periplakin, desmocollin, desmoplakin, desmogleins, BP180 antigen, BP230 antigen, and plectin.

In patients with bullous pemphigoid, pathogenic anti-BP180 IgG autoantibodies are evaluated by ELISA or IIF. A quantitative evaluation should be monitored at days 0, 60, and 150 during treatment. A negative anti-BP180 IgG antibody at day 150 has a good predictive value of durable remission in approximately 90% [5].

In patients with dermatitis herpetiformis, pathogenic autoantibodies are IgA against tissue transglutaminase (anti-tTG) and IgA against endomysia (primate smooth muscle reticular connective tissue, EMA). Tissue transglutaminase (tTG) antigens share a 64% homology with epidermal transglutaminase, which is the target antigen in dermatitis herpetiformis. Detection by ELISA anti-tTG IgA is positive in 90% of patients with dermatitis herpetiformis. Detection of EMA IgA antibody uses IIF and is positive in 100% of patients with dermatitis herpetiformis [6]. Both markers are useful in detection of bowel damage and gluten-free diet compliance in patients with dermatitis herpetiformis and they disappear, if a gluten-free diet is strictly adherent. In general, monitoring of autoantibodies reflect patient's adherence to a gluten-free diet. Serological evaluation is sensitive to detecting major but not minor failure in diet.

Therapy protocol of pemphigus group diseases and pemphigoid diseases is divided into three phases, based on the activity of the disease. The first is the induction phase, followed by a consolidation phase and then a maintenance phase. During the induction phase, control of disease should be established usually by a high dose of immunosuppressant agent, mostly corticosteroids. Bullous disease usually responds to treatment within 2 weeks, provided the correct dose is used. In the consolidation phase, the dropped dose of medication is used until the bulk of lesions have been healed. Slow healing is an indicator that the dose of medication is inadequate and should be boosted. The maintenance phase begins once most lesions have been healed (80%). The rate of medication tapering is based on clinical improvement of the disease and the physician's experience. If new lesions (one to five) appear while medication is tapering, these can be treated with high potency topical or intralesional corticosteroid, while maintaining patients on their current dose of systemic medications. If many new lesions appear, the dose of corticosteroids should be increased in 25–50% increments until control of disease is achieved. In most patients, the healing is slow, often requiring a period of 1–3 months for complete clearance of lesions. Discontinuation of immunosuppressive therapy may be proposed if complete remission is achieved with a low dose of systemic corticosteroid (prednisolone ≤10 mg/day) for a period of 6–12 months. Remission should be supported by negative DIF data. DIF data is a sensitive method for autoantibody detection in tissue in active disease, as well as in remission. Furthermore, DIF data correlate with the immunological activity of the disease. Patients with a higher autoantibody titer and positive DIF data are likely to experience disease relapse. In pemphigus group, the titer of autoantibodies correlates with disease activity, while not so closely in the bullous pemphigoid group, but also is used in monitoring.

The aim of treatment is to suppress disease activity with the minimum dose of drug necessary to induce complete remission, with minimum dose resulting in minimum adverse events, allowing all therapies to be discontinued. Duration of different treatment regimens is not standardized, ranging from 1 to 5 years or even longer. Long-term treatment leads to a high accumulation of corticosteroids and adjuvant drugs, leading to the development of adverse events from all used medications. In general, minimizing potential adverse effects of corticosteroids could be managed by agent that reduces osteoporosis and antacids, following a diet low in sugar and salt. In methotrexate protocol, the bone marrow depression could be reduced with folic acid. It is also important to reduce risk factors such as bacterial or viral infections, sun exposure and radiation therapy, large dental procedure, and psychical stress. In dermatitis herpetiformis, the most preferred precaution is to avoid a diet failure. Physicians and patients should be aware that autoimmune bullous diseases may not require lifelong treatment. However, patients with autoimmune bullous diseases should be monitored in their clinical remission and blood analysis for autoantibody detection. Both help to evaluate the risk of disease flaring up.

3. Systemic treatment of pemphigus group

3.1. Systemic induction therapy

Systemic induction therapy should be started with systemic immunosuppressive medication in combination with topical antiseptic agents and possible topical corticosteroids. Only in

exceptional cases of limited disease and minor severity, monotherapy with topical corticosteroids or with topical calcineurin inhibitors may be considered. However, patient clinical symptoms and the presence of autoantibody level should be evaluated.

Corticosteroids are the mainstay therapy in management of mild to severe disease of all subtypes of pemphigus due to their rapid effects, resulting in a significant improvement in morbidity and mortality rates. Corticosteroids are regarded as a first-line treatment for initial management of pemphigus. Prednisolone equivalent of 0.5–1.5 mg/kg/day is recommended as the initial dose in induction therapy, depending on disease severity, patient age, and comorbidities. To control pemphigus foliaceus, generally, lower doses than that of pemphigus vulgaris are required. If the control of the disease is not achieved within 2 weeks, a higher prednisolone equivalent up to 2.0 mg/kg/day is optional. In severe and recalcitrant disease, a daily dose above 100 mg should be utilized intravenously in pulse therapy mode. Doses of pulse therapy are not standardized. Methylprednisolone 10–20 mg/kg/day (250–1000 mg) is administered every day on 3 consecutive days in intervals of 3–4 weeks, subsequently for 6–8 weeks [7]. Another choice is to use dexamethasone 2–5 mg/kg (50–200 mg). The aim of pulsing is to achieve more rapid and effective disease control compared with conventional oral dosing. However, adverse effects are common and dose related. The dosing schedule is advocated according to disease severity. Patients with mild disease are treated with initial prednisolone equivalent 40–60 mg/day, and more severe cases with 60–100 mg/day. If the patient does not respond within 5–7 days, the dose should be increased in 50–100% increments until disease control is achieved. When a patient does not respond well to systemic prednisolone therapy even at higher doses, the change of prednisolone to other oral corticosteroid (e.g., betamethasone, dexamethasone or methylprednisolone) might improve patient's condition [8]. Autoantibody titers fall with clinical healing, but the decrease of autoantibody titer is slower than clinical improvement.

Systemic corticosteroids can be combined with an immunosuppressive adjuvant agent at the start of therapy, especially in individuals with increased risk of corticosteroid-related side effects (**Table 1**). However, the addition of an adjuvant agent in induction therapy was not exactly confirmed and documented. Adjuvant drugs are usually administered in combination with a systemic corticosteroid to reduce related adverse and side effects and increase the immunosuppressive efficacy of medication. Their corticosteroid-sparing effect may lead to corticosteroid-free remission. If an adjuvant agent is utilized at the induction phase of treatment combined with corticosteroid, its efficacy should be expected in within approximately 1 month, depending on the specific adjuvant drug. Some authorities believe that the time to induce remission is shorter in high dose oral prednisolone monotherapy than with low dose oral prednisolone combined with an adjuvant drug. Moreover, rapidly progressive lesions necessitate a high dose of corticosteroid for early and adequate control of the disease. However, the significantly higher dose directly correlates to increased rates of treatment-associated adverse events. Therapy-related side and adverse effects and complications should be expected in prolonged administration of more than 4 months or at prednisolone dose ≥10 mg/day [1].

In severe and refractory cases, the induction therapy can be started with second-line adjuvant agents' rituximab, intravenous immunoglobulins or by immunoadsorption.

First-line therapy	Dose initial therapy
Prednisolone	0.5–1.5 mg/kg/day
Second-line therapy (first-line adjuvant agent)	
Azathioprine	1–3 mg/kg/day
Mycophenolate mofetil	2 g/day
Mycophenolic acid	1440 mg/day
Third-line therapy (second-line adjuvant agent)	
Cyclophosphamide	500 m i.v. bolus or 2 mg/kg/day orally
Methotrexate	10–20 mg/week
Dapsone	100 mg/day or up to ≤1.5 mg/kg/day
Anti-CD20 monoclonal antibody (rituximab)	2 × 1 g i.v. (2 weeks apart) or 4 × 375 mg/m^2 (each 1 week apart)
Intravenous immunoglobulin G	2 g/kg/4 weeks i.v.
Immunoadsorption	2 cycles a 4 days, 4 weeks apart
Pemphigus herpetiformis	
Dapsone + prednisolone	100–300 mg/day + low dose of prednisolone
IgA pemphigus	
Dapsone + prednisolone	100–300 mg/day + low dose of prednisolone
Acitretin	50 mg/day

First-line therapy uses systemic corticosteroid that has rapid immunosuppressive efficacy. Second-line therapy is used in refractory disease or in contraindications to systemic corticosteroids. First-line adjuvant agents have corticosteroid-sparing effect. Second-line adjuvant agents are used in refractory disease or in contraindications to first-line adjuvant agents.

Table 1. Systemic treatment of pemphigus group.

3.2. Systemic consolidation therapy

Systemic consolidation therapy in pemphigus vulgaris starts as soon as control of disease activity is achieved and approximately 80% of lesions are healed. Tapering of the corticosteroid can start by approximately 25% of the dose at 7–14-days intervals. If tapering reached a prednisolone equivalent of 20 mg/day, slower tapering at 2- to 4-week intervals is recommended. If relapse of the disease develops in the consolidation phase, systemic corticosteroid dose should be returned to two reduction intervals before. If control of disease activity is achieved within 14 days, tapering of corticosteroid can continue. If control of disease activity is not achieved, it is recommended to return to the initial systemic corticosteroid dose [1, 7].

Immunosuppressive efficacy of systemic corticosteroid is enhanced, if combination with other immunosuppressive adjuvant is used, including azathioprine, mycophenolate mofetil, cyclophosphamide, methotrexate or dapsone. Most adjuvant immunosuppressive drugs act more slowly than corticosteroids and their efficacy manifests within several weeks. Therefore, adjuvant agents are most frequently utilized after control of disease activity is achieved.

3.3. Systemic maintenance therapy

In the systemic maintenance phase, systemic corticosteroid is gradually tapering to the lowest level that suppresses the appearance of new lesions, with the goal being to discontinue all medications eventually. If a patient is treated with two or more immunosuppressive drugs, these should be tapered one at a time. Corticosteroid tapering continues from the consolidation phase and other immunosuppressive agents should be tapered later. Tapering too rapidly increases the chance of relapse, while tapering too slowly may lead to medication-related side effects. In complete remission on therapy, the patient receives minimal therapy, i.e., less than 10 mg/day prednisolone and/or minimal adjuvant therapy for at least 2 months. Minimal adjuvant therapy is defined as half of the initial dose. The systemic corticosteroid dose is reduced by approximately 25% at 7 to 14 days and gradual conversion to an alternate day schedule once the daily dose is at 10–8 mg. The rate of medication tapering is based on the clinical outcome and physician's experience. If autoantibody does not continue to fall and new lesions (one to three) appear while medication is being tapered, new lesions could be treated with intralesional or highly potent topical corticosteroid while maintaining the patients on their current dose of systemic medications [9]. The appearance of three to five lesions in a month that do not heal spontaneously within 1 week is regarded to be a relapse of disease in the maintenance phase. The dose of medication should be returned to the dose given two reduction intervals before until control of the disease is achieved.

Remission on minimal maintenance dose, negative autoantibody level, and negative DIF data are indicating markers for discontinuation of immunosuppressive medication. It is recommended to control the DIF data, if the patient is on a minimal maintenance dose for about 6–12 months with total clinical clearance [1]. Healthy skin from the sacral area not irradiated by the sun and covered with suits is a suitable sample for DIF. In addition, discontinuation of medication can ultimately be compassed in most patients. The proportion of patients in whom discontinuation of immunosuppressive therapy can be achieved increases steadily with time, and it can be discontinued in approximately 50% of patients after 3 years and in 75% of patients after 10 years [10, 11].

Prolonged treatment lead to high cumulative doses of corticosteroids and adjuvant drugs and medication-related side and adverse effects.

3.4. Adjuvant drugs

The application of adjuvant drugs into the therapy regimen of autoimmune bullous skin disorders allows the period of high dose corticosteroids application to be shortened. Adjuvant drugs have a corticosteroid-sparing effect, following with a decrease of corticosteroid-related side and adverse effects and an increase in the immunosuppressive efficacy of the regimen. Recently, several adjuvant agents have been utilized as an initial treatment in combination with corticosteroids.

3.4.1. Azathioprine

Among adjuvant agents, azathioprine is regarded as a first-line adjuvant with corticosteroid-sparing efficacy, most frequently used to treat autoimmune bullous disease including

pemphigus. Azathioprine is a purine analog with specific activity to lymphocytes and is more selective for T-cells than B-cells [12]. Azathioprine interferes with purine synthesis and metabolism, leading to delayed action of drug, as it usually takes at least 1–2 months [13].

Extensive experience with azathioprine refers to good efficacy, tolerability and safety profiles. One study compared four regimens in 120 patients with pemphigus vulgaris. The efficacy of prednisolone was enhanced, when the drug was combined with an immunosuppressive adjuvant. Among adjuvants, azathioprine showed the highest corticosteroid-sparing effect. Other compared adjuvants were mycophenolate mofetil, intravenous cyclophosphamide, and prednisolone alone. In general, azathioprine is believed to be more effective than corticosteroid alone, both in terms of mortality and morbidity rates [14]. Another review evaluated 20 clinical studies comprehending data of 826 patients with pemphigus vulgaris and pemphigus foliaceus and confirmed the very good corticosteroid-sparing effect of azathioprine better than cyclophosphamide. However, azathioprine did not increase the remission rate [15]. The next review evaluated 10 clinical studies that comprehended data of 559 participants treated with various adjuvants, including azathioprine, mycophenolate mofetil, cyclophosphamide, intravenous immunoglobulins, plasma exchange and infliximab. All adjuvants collectively decreased the risk of relapse by 29%, but all of them did not increase the remission rate [16]. The corticosteroid-sparing effect of azathioprine was also confirmed in a review study of 11 studies with 404 participants [17].

The activity of thiopurine methyltransferase (TPMT) should be evaluated before the beginning of therapy with azathioprine. Decreased activity of TPMT takes place in induction of an adverse event. In the Japanese population, an adverse event of azathioprine was associated with gene mutation of inosine triphosphate pyrophosphohydrolase (ITPA), another enzyme metabolizing azathioprine [18]. It is recommended to start therapy with a low initial dose of azathioprine 50 mg/day to detect idiosyncratic reactions. If the activity of TPMT shows normal levels, the dose can be increased to 1–3 mg/kg/day depending on the clinical outcome. If TPMT activity shows an intermediate or low level, it should be applied in a lower dose up to 0.5–1.5 mg/kg/day. Patients with insufficiency of TMPT activity are at risk and should not be treated with azathioprine because they may experience rapid bone marrow suppression after initiation of therapy. Furthermore, some patients may experience complications despite normal TPMT activity. All patients at risk of severe toxicity should undergo close monitoring of clinical and hematologic parameters, including liver enzyme levels. Likewise, an abrupt increase in liver enzymes observed soon after administration of azathioprine is a clue to deficient TPMT activity. In addition, concurrent therapy with TPMT-inhibiting drugs, such as allopurinol or sulfasalazine, can also increase the risk of myelotoxicity [19].

If the clinical outcome improves, the lowest effective dosage should be administered. If no improvement occurs within 3 months, the drug should be withdrawn and changed for another adjuvant agent. However, in patients who achieve improvement in clinical outcome, care should be taken in monitoring for myelosuppression and hepatotoxicity. It is strictly recommended to monitor the full blood count weekly over a period of 8 weeks, then at a minimum of once every 3 months. In addition, liver functions should be monitored.

Adverse drug reactions with azathioprine occur in 15–30% of patients and include leucopenia, thrombocytopenia, anemia, pancytopenia, and hepatotoxicity [13]. Long-lasting immunosuppression

increases the risk of infections and only a minor increase of neoplasia, mostly lymphoma [20]. In addition, alopecia, rash or gastrointestinal disturbances (nausea, vomiting, anorexia, diarrhea, aphthous stomatitis, and pancreatitis) can be observed. In pregnancy and breastfeeding, azathioprine is contraindicated due to the risk to the child [21].

Extensive experience with azathioprine refers to good efficacy and safety profile and the drug is recommended as a first-line adjuvant agent with corticosteroid-sparing immunosuppressive in the second line of treatment in moderate to severe pemphigus vulgaris and pemphigus foliaceus, and other types of pemphigus.

3.4.2. Mycophenolate mofetil and mycophenolic acid

Mycophenolate mofetil is an esterified prodrug of mycophenolic acid. Both belong to first-line adjuvants. Mycophenolic acid is an active metabolite that selectively inhibits inosine monophosphate dehydrogenase, an enzyme involved in *de novo* synthesis of quanosine nucleotides. Mycophenolate mofetil inhibits T-cells and B-cells proliferation, and antibody production by B-cells [22]. The induction of disease remission often requires at least 8 weeks of treatment.

One study compared combined therapy of corticosteroid with mycophenolate mofetil or azathioprine. Both adjuvants demonstrated similar efficacy, sparing effect, and safety profiles [23]. Very good efficacy was demonstrated in 18 patients with pemphigus vulgaris treated with mycophenolate mofetil using a conventional dose, with 89% of them achieving complete disease control. The average time to achieve 75% clearance of lesions was 4.5 months. Three patients discontinued all immunosuppressive therapy, including mycophenolate mofetil, in an average of 3 years [24]. Another review of 11 clinical studies comprehended data of 404 patients with pemphigus vulgaris and pemphigus foliaceus and evaluated mycophenolate mofetil as more effective in achieving disease control than azathioprine [17]. Mycophenolate mofetil is regarded to be less myelosuppressive and hepatotoxic than azathioprine [20].

Adverse drug reactions include especially gastrointestinal events such as diarrhea, nausea, vomiting, following with infections, leucopenia, and anemia. Hematologic findings are dose-related and reversible. In general, mycophenolate mofetil is well-tolerated and serious adverse effects are rarely observed. The recommended dose of mycophenolate mofetil is 0.5–2 g/day or mycophenolic acid at 1440 mg/day. However, increasing the daily dose by 1 capsule (500 mg) per week is recommended until the final dose of 2 g/day to evoke better gastrointestinal tolerance. Enteric-coated mycophenolate sodium was prepared to minimize gastrointestinal side effects and improve quality-of-life and compliance to treatment [25]. Mycophenolate mofetil is contraindicated in pregnancy because of the increased risk of miscarriage and congenital malformations [21]. Mizoribine is a newly developed immunosuppressive agent affecting purine synthesis similar to mycophenolate mofetil and can be utilized in patients with autoimmune bullous diseases, including pemphigus vulgaris [26]. It is suspected that mizoribine would have lower toxicity and higher tolerability than other immunosuppressants, such as azathioprine or cyclosporine.

Mycophenolate mofetil displayed a very good safety and efficacy profile as a first-line adjuvant agent and could replace azathioprine as an antimetabolite adjuvant of choice in the

second-line treatment of many autoimmune and inflammatory diseases, including moderate to severe pemphigus vulgaris and pemphigus foliaceus as well as other types of pemphigus.

3.4.3. Cyclophosphamide

Cyclophosphamide is a second-line adjuvant agent that can be utilized when first-line adjuvant agents fail to evoke remission or a corticosteroid-sparing effect. Cyclophosphamide is an alkylating agent with highly effective immunosuppressive activity. It alkylates DNA at various positions, resulting in cell cycle arrest, DNA repair, and apoptosis. Proliferating tissues with a high mitotic rate are the most susceptible to cyclophosphamide. However, its activity is not cell cycle-dependent. Both cellular and humoral immunity is suppressed [27]. The toxicity is significantly higher than that of azathioprine and therefore it is reserved for the most severe and refractory diseases.

Several studies demonstrated that oral cyclophosphamide is an effective adjuvant in the treatment of severe and refractory pemphigus vulgaris and pemphigus foliaceus in dose 2–2.5 mg/kg/day each morning followed by massive oral hydration of at least 2–3 L of fluids [28]. One retrospective study evaluated therapy in 101 patients with pemphigus vulgaris. Authors compared oral cyclophosphamide, azathioprine, and cyclosporine. Cyclophosphamide was evaluated as the drug with the best remission and relapse rates [29]. Another comparative study of 16 patients with pemphigus vulgaris showed a faster onset of activity in cyclophosphamide than azathioprine, but the evaluation of efficacy in both did not differ [30]. One prospective study of 11 patients with pemphigus compared dexamethasone-cyclophosphamide pulse therapy with oral corticosteroid (methylprednisolone)-azathioprine therapy in conventional doses and failed to find significant benefits between these two regimens, besides fewer recurrences in pulse therapy with cyclophosphamide [31]. Cyclophosphamide showed a very good corticosteroid-sparing effect [29].

Several dosing schedules have been developed to minimize cumulative dose and susceptibility to adverse events. These include monthly intravenous administration (500 mg) in conjugation with low oral dose daily between infusions (2.0 mg/kg/day). A single dose of intravenous immunoablative therapy can also be used. However, daily oral cyclophosphamide results in the highest cumulative dose. On the other hand, continuous daily exposure provides optimal immunosuppression. In severe recalcitrant pemphigus vulgaris, a combined regimen of pulsed intravenous cyclophosphamide with corticosteroid could be used. The pulse regimen consists of the intermittent administration of a high dose of corticosteroid and cyclophosphamide, usually as three daily doses of corticosteroid (dexamethasone 100 mg or methylprednisolone 500–1000 mg) and a single dose of cyclophosphamide (500 mg). Such corticosteroid-cyclophosphamide pulses can be administered once a month over a period of several months. Between these pulses, the patient receives cyclophosphamide 2 mg/kg/day.

In cyclophosphamide therapy, adverse events are frequent, including hemorrhagic cystitis and high susceptibility to infection. Mutagenic activity increases an individual's lifetime risk for transitional cell carcinoma of the bladder and hematologic malignancies. This risk is proportional to the cumulative dose of the drug. Moreover, acute myelosuppression can be developed in 6–10 days and recovered in 14–21 days after discontinuation of cyclophosphamide.

However, another adverse gastrointestinal event may develop, including mucosal ulcers, nausea, vomiting, stomach pain, and diarrhea. Potential gonadal toxicity is associated with amenorrhea, azoospermia, and infertility [19]. In addition, cardiotoxicity, hepatotoxicity, interstitial lung fibrosis, darkening of the skin and nails, alopecia, changes to hair color and texture, and lethargy may develop.

The efficacy and safety profile raised cyclophosphamide as a second-line adjuvant drug of choice in the third line of treatment in severe and refractory pemphigus vulgaris and pemphigus foliaceus.

3.4.4. Methotrexate

Methotrexate was primarily developed to treat malignancies. Recently, methotrexate has been used as an immunosuppressive and anti-inflammatory agent. Methotrexate is a folate antagonist that competitively inhibits dihydrofolate reductase, resulting in blocking of several folate-dependent enzymes integral to DNA synthesis. The synthesis of purine and pyrimidine nucleotides is involved, which in turn is necessary for synthesis of DNA and RNA. The drug affects the S-phase of the cell cycle, thus inhibiting rapidly proliferating cells, including malignant, hematopoietic, and mucosal [32]. However, methotrexate inhibits cell proliferation especially at higher doses. At lower doses, the drug has anti-inflammatory activity. The mechanism of anti-inflammatory activity is not fully understood. It could be mediated via a pathway separate from folate antagonism. The drug may evoke the inhibition of polyamines, resulting in a net increase in intracellular and extracellular adenosine. Adenosine is a purine nucleoside with potent anti-inflammatory effect on many different target cells [32, 33].

Methotrexate was the first adjuvant drug to be combined with corticosteroid in the management of autoimmune bullous diseases. A retrospective analysis of 7 clinical studies evaluated the efficacy of methotrexate in 116 patients with pemphigus vulgaris. Of those, 83% showed clinical improvement. Fourteen patients achieved total remission and were off therapy by a mean of 2.6 years after discontinuation of methotrexate and systemic corticosteroid. Nausea and infection were the most frequent side effects and one patient died due to bronchopneumonia [34].

At present, a methotrexate dose of 10–20 mg/week is used orally to treat autoimmune bullous diseases, including pemphigus vulgaris. A test dose of 2.5–5 mg is recommended at the initiation of therapy. If the drug is tolerated, the dose can be escalated to the therapeutic dose. Methotrexate has good oral bioavailability and is akin to parenteral administration. However, interindividual absorption variability exists. Therefore, in patients with an inadequate answer to oral administration, a switch to intramuscular dosing is recommended. Folic acid is used to decrease the deleterious side effects of methotrexate and can be used the next day in a dose of 1–5 mg or daily. Folic acid supplementation can prevent folate deficiency, improving tolerance and preventing anemia, neutropenia, stomatitis, and oral ulcers. Methotrexate is a corticosteroid-sparing agent with delayed, beneficial effect on oral lesions, whereas the cutaneous lesions usually respond very well and rapidly. Methotrexate may interact with nonsteroidal anti-inflammatory drugs, trimethoprim-sulfamethoxazole, sulfasalazine and phenytoin, resulting in increased time to eliminate methotrexate. These interactions may result in severe bone marrow toxicity. Adverse events

involving methotrexate are usually mild and self-limiting or preventable. When an adverse event occurs, the dosage should be decreased or withdrawn. In a relatively brief time, the adverse effects may consolidate in a normal condition. The most frequent adverse effects include nausea, anorexia, vomiting, diarrhea, fatigue, and malaise. Fatigue and nausea may be minimized by taking the drug before bedtime and by folic acid supplementation. In general, adverse effects are dose-dependent and usually appear around the initiation of therapy. A serious adverse event is myelosuppression, which can develop in patients with potential risk factors like renal insufficiency, senescence, concomitant serious illness or infection, drug overdose or drug interaction. In severe cases, myelosuppression is considered a potentially fatal condition, but usually improves after dose reduction or withdrawal. Mucositis is regarded as precursor of developing pancytopenia, and should be taken seriously. Patients with significant pancytopenia (WB ≤ 3000, Hg ≤ 11, platelets ≤ 50,000) should be treated immediately with intravenous leucovorin (folinic acid), the antidote to methotrexate, that is able to bypass dihydrofolate reductase [35]. In addition, hepatotoxicity, resulting in fibrosis and cirrhosis, is a serious adverse event associated with long-term administration of methotrexate, when the cumulative dose reached 9.5–26 g [34]. Obesity, diabetes mellitus and excessive alcohol consumption are regarded as risk factors for liver toxicity. According to the Manchester protocol, serum procollagen III aminopeptide (PIIINP) assay may be used to monitor liver toxicity resulting from methotrexate toxicity [36]. If PIIINP assay is not approachable, some authors predict a liver biopsy. A liver biopsy is recommended when the total cumulative dose reaches 3.5–4.0 g [37]. Monitoring of liver function and bone marrow is recommended to be repeated regularly to avoid myelosuppression and hepatotoxicity. Methotrexate is contraindicated in pregnancy due to its teratogenic and abortifacient properties. Moreover, it causes reproductive toxicity and decreases the sperm account [38]. Mucocutaneous toxicity occurs more commonly in patients without adequate folic acid supplementation. In severe cases, it can be associated with diarrhea and myelosuppression. Mucocutaneous toxicity can start with mucositis or very painful oral ulceration. More rarely, ulceration of the skin could be an early harbinger of methotrexate toxicity.

Methotrexate is a corticosteroid sparing agent and is recommended as a second-line adjuvant in the third-line treatment of moderate to severe pemphigus vulgaris and pemphigus foliaceus. The drug is relatively inexpensive.

3.4.5. Dapsone

Dapsone is a sulfone-derived drug that primarily possesses both antimicrobial and antiprotozoal activities. Additionally, dapsone has anti-inflammatory properties like non-steroidal anti-inflammatory drugs. Dapsone suppresses neutrophilic infiltration by inhibition of neutrophil activation and recruitment through many different pathways [39].

One multicenter randomized, double blind study confirmed the glucocorticoid-sparing efficacy of dapsone in 19 patients with pemphigus vulgaris. Seventy-three percent of patients treated with dapsone achieved remission [40]. A retrospective review study analyzed 35 case series and case reports comprehending data of 427 patients with autoimmune bullous disease. Among them were 55 patients with pemphigus (32 patients with pemphigus vulgaris and 14 with pemphigus foliaceus). Dapsone was evaluated as an effective and useful corticosteroid-sparing

agent in therapy of autoimmune bullous disease, including pemphigus. Adverse events were dose-dependent and reversible. The most frequent adverse event was hemolysis and concomitant anemia secondary to hemolysis [41].

The recommended dose of dapsone is 100 mg/day or up to ≤1.5 mg/kg/day. Prior to start dapsone therapy, glucose-6-phosphate dehydrogenase deficiency should be excluded, and cell blood counts, renal and liver functions must be examined. During dapsone therapy, cell blood counts including reticulocyte, leukocyte and platelet, and the level of methemoglobin, should be regularly monitored. It is recommended to start dapsone therapy with a low dose of 0.5 mg/kg/day. If the drug is tolerated, the dose can escalate slowly up to the effective dose [39]. A rapid enhancement of medication may result in a severe hemolytic anemia. Adverse events are dose-dependent and transient. However, frequent adverse effects include hemolytic anemia and methemoglobinemia which may necessitate halting treatment. A high dose of vitamin C supplementation can evoke better tolerability of dapsone, including a drop in the methemoglobin level. In addition, headache is a common adverse event. More serious complications are hepatitis, hypersensitivity syndrome and agranulocytosis. Peripheral neuropathy is a rare adverse event and may involve both motor and sensory nerves [39]. Most complications are referred in the first 3 months of treatment. Precaution should by mentioned in the second trimester of pregnancy, when dapsone should be reduced or stopped. If dapsone is not tolerated, it could be replaced with other sulfonamides, e.g., sulfapyridine (1.5 g/day) or sulfamethoxypyridazine (0.25–1.5 g/day). In addition, sulfonamides are contraindicated in breastfeeding women because they may induce hemolytic anemia in an infant.

Dapsone is recommended as a second-line adjuvant agent to treat mild to severe pemphigus vulgaris and pemphigus foliaceus, especially in the maintenance phase of their management. The drug is a corticosteroid-sparing agent recommended with either low or intermediate doses of systemic corticosteroid and may allow tapering or discontinuation of corticosteroid doses. Dapsone is regarded as a third-line therapy in pemphigus diseases.

3.4.6. Anti-CD20 monoclonal antibody (rituximab)

Rituximab is a murine/human chimeric monoclonal antibody, targeting the CD20 molecule found on the cell surface of B-cells of various maturate stages up to the preplasma cell stage. Stem cells or B-cell progenitors, plasmablasts, and plasma cells, do not express the CD20 molecule and do not respond to rituximab. Among several mechanisms involved in pathophysiology of autoimmune bullous disease, rituximab exerts B-cell cytotoxic activity mainly through antibody-dependent cell-mediated cytotoxicity, resulting in depletion of B-cells that presumably produce pathogenic antibodies. Depletion of B-cells persists in circulation for 6–12 months. However, after the rituximab treatment, the B-cell count returns to normal levels. Even so, replacement of B-cells is not associated with relapse in a considerable number of patients with autoimmune disease. These data suggest that rituximab-mediated depletion of B-cells may influence also other cells participating in immune tolerance and homeostasis. In addition, the depletion of B-cells may participate in decreasing resistance against infection. One study demonstrated a significant reduction of T regulatory cells after rituximab therapy. This event may be due to increased skin homing of these cells [42].

Primarily, rituximab was used for treating non-Hodgkin's B-cell lymphoma. The use of rituximab in pemphigus began after a marked improvement in lymphoma-associated paraneoplastic pemphigus [43]. Rituximab has a late onset of action to control acute disease and produces an initial clinical response in 69 weeks or less. It should therefore, be used as an adjuvant agent combined with systemic corticosteroids and/or another adjuvant agent. Two FDA protocols for rituximab management can be used to treat autoimmune bullous disease, including pemphigus. The lymphoma protocol utilizes four infusions of rituximab 375 mg/m^2 given in four consecutive weeks, a week apart. The rheumatoid arthritis protocol uses two infusions at a dose of 1 g, given 2 weeks apart. Even though both protocols are effective, the rheumatoid arthritis protocol could prove better because both rheumatoid arthritis and pemphigus are autoimmune diseases. One retrospective review report evaluated 42 clinical studies comprehending data of 272 patients with pemphigus vulgaris who have been treated with rituximab. Data of the review study showed that a complete remission was achieved in 66.6% of patients on the lymphoma protocol and 75% on the rheumatoid arthritis protocol within an 18-month follow-up. During this period, 11.1% of patients treated with the lymphoma protocol achieved remission and were off therapy and 33.3% on minimal immunosuppressive therapy. Meanwhile, on the rheumatoid arthritis protocol, 53.3% of patients achieved remission off therapy and 17.4% on minimal immunosuppressive therapy. A partial response was observed in 12.8% of patients on the lymphoma protocol, and in 23.9% of patients on the rheumatoid arthritis protocol. The relapse rates were 22.8% on the lymphoma protocol and 35.9% on the rheumatoid arthritis protocol. The incidence of serious infections was 3.9% on the lymphoma protocol and 15.2% on the rheumatoid arthritis protocol. The mortality rate on the lymphoma protocol was 2.2% and 1.1% on the rheumatoid arthritis protocol [44]. Remarkable differences were observed in patient's response between both protocols. At present, the reason for protocol differences cannot be detected. Rituximab has a corticosteroid-sparing effect. In the future, a modified protocol for autoimmune bullous disease should be designed and evaluated. Some patients can develop resistance and do not respond to the rituximab regimen. The resistance can be due to the autoantibody to rituximab that interferes with drug binding or the pharmacokinetics of the drug could be changed by other ways.

Intravenous administration of rituximab should be initiated with premedication before each infusion using an antipyretic, e.g., paracetamol 1000 mg orally, or antihistamine. Prior to the first infusion, prednisolone 100 mg orally is advised. Rituximab infusion should be administered over 4–5 h. One cycle of rituximab may be repeated. Pathological lesions start to heal within just a few weeks after the first rituximab infusion and maximal effect can be expected after 3–4 months. Remission rates after the first-treatment cycle reached 76%. Repeating treatment further increased the remission rates to 91% [45].

Rituximab is generally well tolerated, and serious adverse effects are rare. Infusion-related reactions include anaphylaxis, hypotension, fever, chills, headache, weakness, nausea, pruritus and rash. Infusion-related reactions could be ameliorated by premedication before each infusion, then by decelerating or temporarily stopping of infusion. In addition, deep venous thrombosis of the lower limb and pulmonary embolism are serious complications. A frequent adverse event is the infection afflicting around 30% of patients, with a larger account of bacterial than viral infections. Moreover, herpes zoster is reported in several cases. Higher rates of infection could be influenced by concomitant treatment with an immunosuppressive agent, including corticosteroids. Another

serious adverse event may accompany rituximab treatment like *Pneumocystis carinii* infection causing pneumonia or septic shock, which may cause death.

In addition, rituximab is an effective drug in controlling recalcitrant disease and is recommended as the second-line adjuvant to treat severe refractory autoimmune bullous diseases, including pemphigus vulgaris, pemphigus foliaceus and pemphigus paraneoplastic. Complications such as fatal infections and other serious adverse events place the drug to the last resort treatment restricted for severe and refractory cases. Rituximab is recommended when other second-line adjuvant agents, including immunoadsorption and intravenous immunoglobulins, fail in the treatment or patients have multiple relapses. Despite the threat of serious adverse events, several reports would like to recommend rituximab as a first-line treatment accompanied with low dose of corticosteroids in patients with moderate to severe pemphigus [46]. The regimen proved effective and caused fewer adverse events than the regimen using corticosteroids alone [47]. First-line treatment with rituximab should be regarded in pemphigus patients, who are contraindicated to corticosteroid and other immunosuppressive therapy [47–49]. In near future, a new protocol for pemphigus patients should be elaborated and confirmed in clinical trials. Another study recommended rituximab combined with intravenous immunoglobulins as a first-line therapy in severe and refractory pemphigus. This regimen can evoke prolonged remission and could be used when corticosteroids and immunosuppressive adjuvants are contraindicated [50].

Research into biologic agents discovered new molecules that could be used in the management of autoimmune bullous diseases. New humanized anti-CD20 monoclonal antibodies modify or bind to different sites to the target molecules. The new molecules escalate activity and possess a higher efficacy in preclinical trials. All of them are of second or third generations of humanized anti-CD20 monoclonal antibody. Furthermore, efficacy, safety, and tolerability should be evaluated in clinical trials. Among them, veltuzumab is an anti-CD20 monoclonal antibody that is largely identical to rituximab. Its advantage is subcutaneous administration. Obinutuzumab possesses 50-fold greater binding and stronger induction of apoptosis than rituximab resulting in a rapid and profound B-cell depletion during the first infusion. Ofatumumab possesses a superior and longer-lasting cytotoxic effect than rituximab. It is used intravenously. Ocaratuzumab has a higher binding affinity and 10-fold higher cytotoxicity, which results in smaller dosage using subcutaneous administration. PRO131921 has 30-fold higher binding affinity and 10-fold higher cytotoxicity than rituximab. It is used intravenously [51]. New humanized anti-CD20 monoclonal antibodies require further clinical trials to evaluate and establish dosing, efficacy and safety, including the monitoring of potential adverse events.

According to the guidelines rituximab is recommended as a second-line adjuvant for severe and refractory pemphigus vulgaris. Rituximab can be utilized, when the failure of conventional therapy is present, e.g., severe adverse events in conventional therapy, contraindications to use a high dose of other immunosuppressive therapies and progressive and rapid uncontrolled disease. Rituximab is regarded as a third-line therapy in pemphigus diseases.

3.4.7. Intravenous immunoglobulin G

Primarily, high intravenous immunoglobulin G was used to treat primary immunodeficiencies, immune thrombocytopenic purpura, Kawasaki disease, chronic B-cell lymphocytic leukemia,

pediatric AIDS and others. In recent years, intravenous immunoglobulin has been used in the treatment of autoimmune and chronic inflammatory diseases, including autoimmune bullous diseases.

Immunoglobulin preparations are a special type of biologic treatment obtained from the pooled plasma of multiple healthy donors amounting 3000–10,000. Purified, pooled plasma contains natural antibodies of the IgG subclass. Natural autoantibodies are believed to play a role in maintaining immune homeostasis. Moreover, it contains a repertoire of the all IgG antibodies from populations as a mirror of the interaction of intravenous immunoglobulin individuals with external pathogens. Plasma may contain also natural autoantibodies, which presents the risk of preparation, but a considerable number of donors assists in dilution of these molecules. In addition, pooled plasma may contain a minimal refused amount of IgA or IgM. The guidelines for processing plasma are precise and stringent to avoid especially viral and bacterial contaminations. For this reason, pooled plasma is stored for 60 days and donors are checked for seroconversation to several pathogens. Individual plasma is also examined by polymerase chain reaction (PCR) for the presence of HCV RNA, HBV DNA, HIV RNA, HAV RNA and Parvovirus B19 DNA [52]. Only plasma with no pathogens may be collected to the pool preparation. Pulled plasma is evaluated for the main biological and pharmacological properties, the degree of purity and the antibody spectrum. The half-life of intravenous immunoglobulin is approximately 3 weeks.

The mechanism of intravenous immunoglobulin assesses several activities involving in activity complex. The desired response of intravenous immunoglobulin is a rapid decline in pathogenic autoantibodies and improvement of disease. The intravenous immunoglobulin produces complement blockade and degradation, Fc-receptor blockade and induces immunomodulatory Fc receptors, inhibits B-cells, and alters T-cell function, modulates cytokine production and cellular migration [53, 54]. Anti-idiotypic antibodies of intravenous immunoglobulin bind to the pathogenic autoantibodies, helping in their rapid decline. Despite partial knowledge of the intravenous immunoglobulin activity, the objective mechanism is not fully understood as it possesses multiple modes of action related to its ability to interact with both innate and adaptive compartment of the immune system [55]. The intravenous immunoglobulin appears to have increased clearance of pathogenic IgG autoantibodies, but failed in the suppression of autoantibody production. However, intravenous immunoglobulin is an adjuvant treatment and suppression of autoantibody production is operated by corticosteroids and other immunosuppressive adjuvants.

The good efficacy and safety profile of intravenous immunoglobulin was documented in multiple reports, mostly small series. The first multicentric, randomized, placebo-controlled, double-blind trial of intravenous immunoglobulin confirmed objectively the efficacy of intravenous immunoglobulin in 61 patients with pemphigus and confirmed a decrease in the autoantibody level in treated patients. After 7 days, anti-Dsg antibody clearance was documented in 42–74.4% of patients [56]. One review study evaluated 23 clinical studies and comprehended data of 260 patients with autoimmune bullous disease treated with intravenous immunoglobulin, among them 191 patients with pemphigus. The intravenous immunoglobulin showed improvement in 245 patients and demonstrated a corticosteroid-sparing effect [57]. In addition, many studies confirmed intravenous immunoglobulin therapy to have a very good safety profile [58, 59].

Some authors offer intravenous immunoglobulin not only for severe and refractory pemphigus vulgaris but also for mild and recalcitrant cases of pemphigus foliaceus [60]. Intravenous immunoglobulin may trigger the shift from an intractable condition to remission using a yet not fully understood mechanism, possibly based on immunomodulation. In recalcitrant pemphigus, a combination of intravenous immunoglobulin and rituximab is recommended. This combination could be useful, when response fails to a high corticosteroid dose in combination with adjuvant immunosuppressive drugs. The mechanism of combined activity of both medications is not known and should be elucidated. However, rituximab affects pathogenic B-cells and blocks production of pathogenic autoantibody and intravenous immunoglobulin rapidly declines pathogenic autoantibody and influences the innate and adaptive immune system. A 10-year follow-up study reported long-lasting remission, in 10 patients with refractory pemphigus vulgaris who have been treated with rituximab combined with intravenous immunoglobulin [9]. The intravenous immunoglobulin preparations are safe and effective and can treat juvenile autoimmune bullous diseases including pemphigus [61]. Several studies reported good safe and efficacy profiles also in pregnancy [38, 62].

An intravenous immunoglobulin response is rapid and administration should be repeated after 4 weeks initially. If the clinical response is good, the interval between cycles could be increased gradually to 6 weeks. If the patient does not respond to an intravenous immunoglobulin therapy, it should be discontinued. In pemphigus vulgaris, the recommended dose is 2 g/kg divided over 3–5 consecutive days. The number of intravenous immunoglobulin cycles should be repeated depending on the severity of disease. In standard regimen, 3–5 cycles are recommended to achieve the desired response. However, severity of the disease may require further intravenous immunoglobulin cycles, without restriction. A repeated dose can be applied also in relapse of the disease. The intravenous immunoglobulin is a relatively safe and well-tolerated therapy. Premedication with an antipyretic, e.g., acetaminophen or antihistamine is recommended to avoid adverse events. Oral or intravenous corticosteroid may be useful, if patient has had a prior reaction or is of elevated risk. The intravenous immunoglobulin should be administered as a long-lasting infusion over 4–5 h.

Systemic adverse events are relatively common, occurring in 20–40% of patients [63], but are mild and most frequently treatable. Immediate adverse reactions account for 60% of all adverse events. They occur during or within 6 h of the infusion and could be avoided by long-lasting infusion. Discontinuation of drug administration may treat immediate adverse events or the treatment is symptomatic. The most frequent immediate adverse event is headache (8.9–43.8%) [63]. Others include muscles aches, fatigue, chills, and fever. Delayed adverse reactions develop within more than 6 h to 1 week after administration. Very rare events occur weeks and months after infusion [63]. A serious adverse event is acute renal failure developing in patients with renal insufficiency. Risk patients are diabetics, older individuals, or patients using concomitantly nephrotoxic agents. Sucrose-free intravenous immunoglobulin preparations are recommended to prevent acute renal failure in risk patients. In these risk patients, an intravenous immunoglobulin should be administered very slowly and at the lowest effective dose. Another serious adverse event is thromboembolism associated with a large dose administered during a fast infusion, which may cause high plasma viscosity. A low dose of intravenous immunoglobulin is imperative also to respect precaution to avoid plasma viscosity.

Thromboembolism may develop within hours, days, or weeks. Risk patients should be monitored. A very rare and serious adverse event is aseptic meningitis, which may develop within 6 h to 1 week [64]. A minimal amount of IgA intravenous immunoglobulin may evoke the production of anti-IgA antibody in patients with IgA deficiency. Subsequently, anti-IgA antibody can cause immediate anaphylactic or anaphylactoid reactions. An intravenous immunoglobulin administration may lead to mild hemolytic reactions, due to the presence of anti-A or anti-B isoagglutinins. Furthermore, mild neutropenia and hyponatremia may occur 2–4 days after infusion and resolves in less than 1 week [63].

Intravenous immunoglobulin is a second-line adjuvant agent and is utilized with corticosteroids or other immunosuppressive adjuvant in refractory pemphigus vulgaris and pemphigus foliaceus. Indication criteria for intravenous immunoglobulin use include the failure of conventional therapy, including significant adverse events in conventional therapy, contraindications to high doses of other immunosuppressive therapies and progressive and rapid uncontrolled disease. However, in exceptional cases intravenous immunoglobulin can be utilized as a first-line treatment, e.g., aseptic bone necrosis, poorly controlled diabetes, advanced osteoporosis, and cataracts. Intravenous immunoglobulin is regarded as a third-line therapy in pemphigus diseases.

3.4.8. Immunoadsorption

Immunoadsorption is a specific method used to selectively clear pathogenic autoantibodies from the circulation in autoantibody-mediated disease, including autoimmune bullous diseases. Immunoadsorption is most frequently used to treat severe and refractory pemphigus vulgaris. In addition, immunoadsorption also removes immune complexes and produces cytapheresis by removing inflammatory cells or platelets from the peripheral circulation. In dermatology, the last can be used to treat pyoderma gangrenosum and psoriasis [65, 66]. Rapid removal of autoantibodies is performed extracorporally by adsorber system, which contains a high-affinity IgG adsorber or low-affinity IgG adsorber. Both adsorber systems differ with respect to ligands, matrix, volume of columns, affinity to certain immunoglobulin classes, and reusability. Reusable adsorbers can be utilized several times for the same patient. The reusable adsorbers are: Immunosorba® (ligand: ligand Staphylococcal protein A), Ig-Therasorb® (ligand: polyclonal anti-human antibodies from sheep), and Globaffin® (ligand: synthetic peptide-PGAM146). Reusable adsorbers are very effective and produce approximately similar depletion rates [67]. A number of one-time adsorbers are available, including adsorber Selesorb® (ligand: dextransulfate), Prosorba® (ligand: Staphylococcal protein A ligand), adsorber IM TR350® (ligand: tryptophan) and IM PH350® (ligand: phenylalanine), and adsorber Coraffin® (ligand: combination of synthetic peptides). One-time use adsorbers achieve only a low degree of IgG decline and usually show little specificity. In the induction phase of therapy, a high-affinity adsorber is recommended. Autoantibody levels can drop by about 75% utilizing a single procedure with a reusable adsorber system. A decrease about of 95% can be reached at the end of one cycle; 3 procedures applied over 3 consecutive days. The 3-day procedure is necessary to avoid a rebound phenomenon, which can appear after the first procedure within 24 h. Autoantibodies re-diffuse from the tissue to circulation and may reach 40% of the initial autoantibody level [68]. In selected cases, the induction phase could be realized with two consecutive treatments with

low-affinity adsorbers (e.g., IM TR350® and IM PH350®). This procedure is utilized in individuals with known hypersensitivity towards material used in columns or other materials. After reaching control of disease, the therapy protocol may continue with subsequent regimen depending on clinical outcome. Single immunoadsorption can be utilized in weekly intervals and later in longer intervals. Another modality is to use a 3- to-4-day procedure repeated monthly. In pemphigus patients, the level of anti-Dsg IgG autoantibody should be evaluated regularly before and after each individual procedure using ELISA or the titer in indirect immunofluorescence. For pemphigus, a new adsorber system is developing with new highly specific adsorber selectively binding anti-Dsg IgG antibodies. Recombinant full-length Dsg1 and Dsg3 ectodomains could be used as a ligand in a highly specific adsorber system [69].

In general, immunoadsorption is recommended to treat severe autoimmune disease, including pemphigus vulgaris in combination with immunosuppressive medication, which can decrease the production of pathogenic autoantibodies. A retrospective study evaluated data of 82 patients with pemphigus treated with immunoadsorption. In most patients, reusable systems were applied with corticosteroids combined with other immunosuppressive drugs, usually azathioprine, mycophenolate mofetil, or cyclophosphamide used in conventional doses. Immunoadsorption showed a sharp decline of anti-Dsg IgG autoantibodies followed by clinical improvement [70]. The recent combination of immunoadsorption with rituximab and immunosuppressive adjuvants azathioprine or mycophenolate mofetil showed complete remission in 88% of patients with autoimmune bullous diseases, including pemphigus vulgaris (6 patients). The combination regimen evokes long-lasting improvement in disease outcome. However, the relapse rate was 13% with an average follow-up of 22 months [71]. In addition, another recent protocol used immunoadsorption combined with rituximab and dexamethasone pulses in conjugation with azathioprine or mycophenolate mofetil, all medication used in conventional doses. Autoantibody levels declined by more than 50% between the first two cycles. This combined regimen demonstrated a long-lasting complete remission in 83% of patients. However, at follow up of 11–43 months a relapse occurred in 26% of patients. In general, the therapy was well tolerated. However, severe adverse events were documented in 9% of patients, including Staphylococcal sepsis and transient paraplegia of the legs [72]. Immunoadsorption combined with another immunosuppressive medication showed a corticosteroid-sparing effect.

Adverse events in immunoadsorption are rare and may occur in ≤1% of procedures [68]. Some severe adverse effects were referred, including deep venous thrombosis, perforating diverticulitis, and sepsis [72]. Other adverse effects may develop such as hypotension, bradycardia, citrate-induced paresthesia, and hypocalcemia [67]. Contraindications for immunoadsorption include known hypersensitivity towards material used in the columns, treatment with ACE inhibitors and anticoagulants, severe cardiovascular disease, hypofibrinogenemia, severe systemic infection and body weight under 15 kg.

Immunoadsorption is a second-line adjuvant treatment in autoimmune bullous disease, including pemphigus. Immunoadsorption is indicated in acute severe disease, if the first-line treatment proved ineffective or is contraindicated. It is a rapid acting mode of treatment and is recommended if a rapid response is required. It can also be used in chronic refractory disease, if the response to standard treatment is inadequate. Immunoadsorption is almost always

utilized in combination with immunosuppressive agents that reduce the production of pathogenic autoantibodies. Systemic corticosteroids are used in high dose orally or intravenously in bolus and usually are combined with adjuvant immunosuppressant, e.g., azathioprine, mycophenolate mofetil or cyclophosphamide. Immunoadsorption is regarded as a third-line therapy in pemphigus diseases.

3.5. Therapy of pemphigus herpetiformis

Pemphigus herpetiformis is a very rare variant in the pemphigus group. The clinical symptoms resemble dermatitis herpetiformis, but the pathogenic autoantibody IgG is directed mostly against Dsg1 (occasionally against Dsg3 or desmocollin) [73]. In general, the prognosis is more favorable than in pemphigus vulgaris. Furthermore, some cases may progress into pemphigus vulgaris, requiring more aggressive treatment. The therapy regimen of pemphigus herpetiformis differs from that of pemphigus vulgaris. Dapsone 100–300 mg/day is utilized as a treatment of choice and can be combined with low dose of systemic corticosteroids. In some severe disease, improvement of disease could be induced with adjuvant agents that are used to treat pemphigus vulgaris. Several authors referred to the good efficacy and tolerability of adjuvant agents, including azathioprine, mycophenolate mofetil, methotrexate, and cyclophosphamides [74, 75]. In refractory disease, intravenous immunoglobulin and plasmapheresis may improve the clinical outcome [73]. One case series report of 8 patients with pemphigus herpetiformis referred to the minimal clinical improvement of two patients treated with rituximab [74].

3.5.1. Therapy of IgA pemphigus

IgA pemphigus is a very rare variant of the pemphigus group. Disease differs in clinical affliction from those in the pemphigus group, because of the pustular lesions accompanied by vesicular ones. Based on clinical and pathological symptoms, it is divided into two variants: the subcorneal pustular dermatosis type and intraepidermal neutrophilic IgA dermatosis type. Pathogenic autoantibodies IgA are most frequently directed against desmocollin-1 and desmocollin-2, -3. Occasionally, IgA autoantibodies can be directed against Dsg1 and Dsg3 [76]. Dapsone is regarded as a first-line treatment. A dose of 100–300 mg/day may improve clinical symptoms of IgA pemphigus. Dapsone can be combined with a low dose of corticosteroids. Refractory cases could utilize etretinate or acitretin (50 mg/day), which can be used alone or in combination with dapsone [77, 78]. No objective clinical study was performed to demonstrate the efficacy and tolerability of various therapy regimens in IgA pemphigus. All recommendations result from clinical experience and small series or case reports.

3.5.2. Therapy of paraneoplastic pemphigus (paraneoplastic autoimmune syndrome)

Paraneoplastic pemphigus or paraneoplastic autoimmune syndrome is a rare condition with a variety of lesions including florid oral involvement, generalized polymorphous cutaneous rash resembling various skin disorders and pulmonary involvement. Moreover, it is associated with malignant neoplasm, most frequently hematoblastosis like non-Hodgkin's lymphoma, chronic lymphocytic leukemia or thymoma. However, paraneoplastic pemphigus may occasionally accompany benign neoplasia like Castleman's disease

or monoclonal gammopathy. Therapy of paraneoplastic pemphigus is almost always very difficult and suboptimal. The mainstay of therapy is to treat underlying neoplasm. Early detection and complete resection of neoplasm are of paramount importance. Subsequently, the removal of neoplasm reduces the production of autoantibodies released from the tumor. Perioperative intravenous immunoglobulins administration in an obvious dose (2 g/kg/cycle) is recommended to block autoantibody release from the tumor during surgery [79]. In the case of benign neoplasm, surgical removal ameliorates the condition and may induce remission of paraneoplastic pemphigus with contemporary decrease of autoantibodies within 6–8 weeks [80]. In malignant neoplasm, the prognosis is poor and depends on the behavior of malignant tumor and development of severe respiratory failure. The mortality rate is high and ranges from 75 to 90% [80]. The disease may progress despite surgery and chemotherapy. The prognosis of paraneoplastic pemphigus is obviously unfavorable with rapid fatal outcome. Treatment of clinical symptoms of paraneoplastic pemphigus can be started with systemic corticosteroid, prednisone 0.5–1.0 mg/kg. Adjuvant agents with corticosteroid-sparing effect including azathioprine, mycophenolate mofetil, and cyclophosphamide in conventional doses could be used, but they have mostly potentially tumorigenic properties and their utilization in this condition is limited. However, patients are often resistant to all conventional therapies and therefore a new therapy regimen should be sought. The preferred treatment in paraneoplastic pemphigus is rituximab, which could probably reduce the risk of tumorigenicity. Several studies referred to the efficacy of rituximab, and some of them about rituximab combined with intravenous immunoglobulin. In several cases, rituximab was combined with chemotherapy depending on underlying malignancy [81]. Separaliter administration of intravenous immunoglobulin may also ameliorate the clinical outcome of paraneoplastic pemphigus and has a corticosteroid-sparing effect [59]. Reports about treatment efficacy and tolerability in paraneoplastic pemphigus embrace only small series or case reports. In addition, the therapy protocol embraces aggressive immunosuppressive agents and adverse events are the rule, including serious infections; among them sepsis is the most frequent cause of death. Respiratory failure, if evident, is a fatal complication. Other fatal complications may result from underlying neoplasm.

4. Therapy of bullous pemphigoid group

Bullous pemphigoid is the most frequent autoimmune blistering disorder and may last several years in the absence of treatment followed by total remission. The tendency to relapse is obligate and can be evoked with/without any risk factors. In general, the course of bullous pemphigoid is less severe and requires less aggressive treatment than pemphigus vulgaris (**Table 2**). However, a very severe course of bullous pemphigoid is not excluded. Relapse of disease starts with pruritus, consequently followed by skin eruption and occasionally also oral mucosa involvement. Advanced age in patients supports a large list of comorbidities, including cardiovascular, neurological, neoplastic, metabolic and respiratory comorbidities. The concomitant treatment regimen of comorbidities can hardly influence the choice of treatment regimen in patients with bullous pemphigoid.

First-line therapy	Dose initial therapy
Topical corticosteroid	High potency corticosteroid up 30–40 g/day
Prednisolone	0.5–0.75 mg/kg/day
Second-line therapy (first-line adjuvant agent)	
Tetracyclines	Oxytetracycline 2 g/day, doxycycline 200 mg/day
Azathioprine	1–3 mg/kg/day
Mycophenolate mofetil	2 g/day
Mycophenolic acid	1440 mg/day
Dapsone	100 mg/day or up to ≤1.5 mg/kg/day
Methotrexate	10–20 mg/week
Cyclophosphamide	500 m i.v. bolus or 2 mg/kg/day orally
Third-line therapy (second-line adjuvant agent)	
Anti-CD20 monoclonal antibody (rituximab)	2 × 1 g i.v. (2 weeks apart) or 4 × 375 mg/m^2 (each 1 week apart)
Intravenous immunoglobulin G	2 g/kg/4 weeks i.v.
Immunoadsorption	2 cycles a 4 days, 4 weeks apart
Linear IgA dermatosis	
Prednisolone	0.25–0.5 mg/kg/day
Dapsone	100 mg/day
Epidermolysis bullosa acquisita	
Prednisolone	1–1.5 mg/kg/day
Dapsone	25–100 mg/day
Colchicine	0.6–1.2 mg/day
Dermatitis herpetiformis	
Gluten-free diet	
Dapsone	50–150 mg/day

In mild bullous pemphigoid, a topical high potency corticosteroid may control disease. Systemic corticosteroids are used in severe disease; compared with pemphigus in lower doses. Tetracycline has an anti-inflammatory efficacy and can replace corticosteroids in mild bullous pemphigoid. Second-line therapy is used in refractory disease with precaution to comorbidities. The third-line adjuvant agents most frequently are used in severe mucous membrane pemphigoid or epidermolysis bullosa acquisita. Antihistamines are used to eliminate pruritus.

Table 2. The treatment of pemphigoid group.

4.1. Topical and systemic corticosteroids

Bullous pemphigoid can occur as localized or limited disease with mild activity. Potent topical corticosteroids, e.g., clobetasol propionate 0.05% cream or ointment is often successful to achieve remission. A dose up to 30–40 g/day can be administered twice daily to the blisters and erosions and perilesional normal skin. Initial treatment should be tapered 15 days after disease control. The tapering regimen embraces the application of corticosteroid cream or ointment every 2 days in the second month, then twice per week in the third month, and then once per week in the fourth month [82]. In relapse, topical corticosteroid

therapy is increased to the previous level. High-potency topical corticosteroids are also recommended to support healing of more severe disease. Application can cover the whole body, sparing the face. However, administration of high potency corticosteroid to a large body area results in systemic absorption. Despite this, topical application of corticosteroids decreases adverse events of systemic corticosteroids. Topical corticosteroids are recommended in mild disease, especially when localized. However, topical corticosteroids can also be utilized in severe disease as they can decrease the dose of systemic corticosteroids. A large comparative study of 312 patients with bullous pemphigoid demonstrated that mild regimen of topical corticosteroid (10–30 g/day) induced co-equal clinical improvement as that of standard regimen (40 g/day). In addition, a mild regimen of topical corticosteroid allowed a 70% reduction in the cumulative doses of topical potent corticosteroid [83]. Application of topical corticosteroids requires nursing care and should be accompanied by antiseptic bath, bullae count, and bandaging.

Systemic corticosteroids are a mainstay of therapy and are used in lower doses than in pemphigus. Severe bullous pemphigoid is treated with prednisolone 0.5–0.75 mg/kg/day as an initial treatment. Prednisolone dose ≤0.5 mg/kg/day seems to be ineffective. Initial therapy starts with prednisolone 0.5 mg/kg/day and can be increased to 0.75 mg/kg/day only if control of disease is not achieved within 1–3 weeks [84]. The major goal in bullous pemphigoid is reducing the patient's cumulative dose of systemic corticosteroid. During the consolidation phase, the dose of corticosteroid is tapered 15 days after disease control. However, earlier tapering is possible, if the outcome of diseases is favorable. In the maintenance phase, the lowest dose of corticosteroid (prednisolone 0.1 mg/kg/day) should be achieved within 4–6 months after initiation of treatment [82, 85]. If the patient is in remission on maintenance dose for 3–6 months, treatment may be stopped. Total treatment from initiation phase through consolidation phase up to maintenance phase, is usually 9–12 months [82]. In the case of relapse, the previous dose of corticosteroid is recommended.

Topical and systemic corticosteroids are the first-line treatment recommended for mild to severe bullous pemphigoid.

4.2. Adjuvant therapy

In bullous pemphigoid, immunosuppressive adjuvant therapy is used with high precautions and respect to comorbidities. Adjuvants are used when systemic corticosteroids are limited or contraindicated, e.g., in diabetes, severe osteoporosis or cardiovascular disease. However, adjuvant agents have a corticosteroid-sparing effect and their use in the elderly is limited because of adverse events, which are more frequent in this population. Associated treatment of comorbidities can interact with adjuvant drugs and facilitated the involvement of adverse events.

4.2.1. Tetracycline

Tetracycline is recommended as a first adjuvant agent with anti-inflammatory activity confirmed by reduction of collagenolytic activity [86]. Several small series documented good efficacy and safety profiles of tetracycline and nicotinamide to treat mild to severe bullous pemphigoid [86, 87]. The therapy regimen is almost always combined with topical high potency corticosteroids. One randomized controlled study compared doxycycline (200 mg/day) and prednisolone

(0.5 mg/kg/day) for initial therapy in 256 patients with bullous pemphigoid. Therapy with doxycycline was evaluated as a useful alternative to prednisolone [88]. The recommended regimen is oxytetracycline 2 g/day and doxycycline 200 mg/day, both orally. Tetracycline can be used alone or in combination with nicotinamide up to 2 g/day orally. Nicotinamide, the amide derivate of vitamin B has been referred to having several types of anti-inflammatory activity, including inhibition of proinflammatory cytokines [87]. The combination of both may result in ameliorating of anti-inflammatory activity of bullous pemphigoid. The presence of circulating autoantibody after clearance of skin lesions is probably based on anti-inflammatory properties and not on decline of autoantibody production against the basement membrane zone. Tetracycline is regarded as a second-line therapy in pemphigoid diseases.

4.2.2. First-line adjuvant agents: azathioprine, mycophenolate mofetil, methotrexate, and dapsone

First-line adjuvant agents can be used in the same dose as in pemphigus vulgaris and include azathioprine, mycophenolate mofetil, methotrexate, and dapsone [22, 89, 90]. However, a daily dose in the lower range is most frequently effective and better tolerated in elderly patients. A retrospective review evaluated 35 case reports and case series and comprehended data of 170 patients with bullous pemphigoid treated with dapsone alone or combined with corticosteroids. Clinical remission was achieved in 81% of patients. Adverse events were developed in 37% of patients and in 5% of patients required discontinuation of dapsone. The most frequent adverse event was hemolysis and concomitant anemia, both were dose-dependent and reversible [41]. A small series study compared the efficacy and safety of azathioprine and dapsone in 15 patients with bullous pemphigoid. Both drugs were effective and showed an acceptable safety profile [91]. Another small series study compared the corticosteroid-sparing effect of azathioprine and dapsone in 8 patients with bullous pemphigoid. The corticosteroid-sparing effect was moderately higher in dapsone [92]. A retrospective review evaluated 6 studies comprehending data of 79 patients with bullous pemphigoid treated with methotrexate. Clinical improvement was achieved in 94% of patients [34]. Another small series study evaluated 16 patients with bullous pemphigoid treated with methotrexate combined with prednisone. Eight of 16 patients achieved remission off therapy after 25.3 months and during the 5.5 years of follow-up [93]. A retrospective study evaluated data of 70 patients with bullous pemphigoid treated with low-dose methotrexate (5–15 mg/week) combined with short-term high potent topical corticosteroid (clobetasol propionate). The regimen demonstrated very good efficacy and induced clinical improvement in all patients in a mean time interval of 21.9 days. Long-term disease control was achieved in 76% of patients [94]. Cyclophosphamide is a very effective immunosuppressant, but also toxic agent, and so its use in bullous pemphigoid is limited and not generally recommended.

4.2.3. Second-line adjuvant agents: intravenous immunoglobulin G, rituximab, immunoadsorption

Second-line adjuvant agents are used in severe or refractory bullous pemphigoid nonresponsive to corticosteroids or adjuvants of the first line. They must be used with extreme precaution in respect of adverse events. Second-line adjuvant medications are the same as in pemphigus and are utilized by standard rule. However, the number of patients treated with this modality is much lower compared with pemphigus. The efficacy and safety of second-line adjuvants were

referred to in several small series and case reports [89, 90]. One review study evaluated 7 clinical studies and comprehended data of 69 patients with bullous pemphigoid treated with intravenous immunoglobulin. All of the patients showed clinical remission within 14–27 months of post-intravenous immunoglobulin follow-up. In 10 patients, the titer of both anti-BP180 IgG and anti-BP230 IgG autoantibodies showed a gradual decline and non-detectable titer after 11 months and 10 months, respectively. No serious adverse event was documented in all patients treated with intravenous immunoglobulin [57]. Another review study summarized 16 patients with bullous pemphigoid treated with rituximab; among them 14 patients were treated according to the lymphoma protocol and 2 patients according to the rheumatoid arthritis protocol. Complete clinical remission was achieved in 69% of patients and 6% of patients did not show any response. The mortality rate was 19%. Two patients died from sepsis and one from cardiac event [95]. The combination of intravenous immunoglobulin and rituximab showed good efficacy and no serious adverse events in 12 patients with severe and refractory bullous pemphigoid, who did not respond to previous conventional immunosuppressive therapy. Complete clinical improvement was achieved in a mean of 4.6 months and previous immunosuppressive therapy was discontinued. Clinical improvement was correlated with rapid decline of anti-BP180 IgG and anti-BP230 IgG autoantibodies and thereafter remained undetected. The therapy regimen was well tolerated without adverse events, including infections. Ten patients remained in remission in the follow-up at 73.8 months [96]. This regimen could be recommended, if conventional therapy fails. Patients with bullous pemphigoid and elevated level of IgE and eosinophilia who do not respond to conventional therapy regimen could be treated with omalizumab, monoclonal antibody that binds to and declines IgE. It is expected that the anti-BP180 IgE autoantibody could be pathogenic in some individuals [97].

Immunoadsorption can be used in severe refractory autoimmune bullous diseases has shown utilization in bullous pemphigoid not responsive to conventional treatment. Only small case series, or several patients were included into a group of pemphigus patients treated with immunoadsorption. Respectable patients for this regimen are those with markedly elevated levels of pathogenic autoantibodies. Clinical improvement is associated with rapid decline of anti-BP180 IgG and anti-BP230 IgG autoantibodies [67, 68, 70, 98]. Depending on the disease outcome, immunoadsorption can be used in several cycles. Adverse events do not differ from those in pemphigus patients and the incidence is low. One case series study documented good efficacy and safety of immunoadsorption combined with rituximab in various severe and refractory autoimmune bullous diseases, including bullous pemphigoid (3 patients), mucous membrane pemphigoid (3 patients), and epidermolysis bullosa acquisita (1 patients). Concomitant medication with systemic corticosteroids and other immunosuppressive drugs was administered. The clinical improvement was compounded with persistent decrease in both anti-BP180 IgG and anti-BP230 IgG autoantibodies. Complete remission was achieved in all patients and, in one patient, all immunosuppressive therapy was interrupted. Combined therapy proved rapid with long-lasting response, and was well tolerated and produced a corticosteroid-sparing effect [71]. Immunoadsorption is a second-line adjuvant treatment in autoimmune bullous disease including bullous pemphigoid, mucous membrane pemphigoid and epidermolysis bullosa acquisita. These second-line adjuvant agents are regarded as a third-line therapy in pemphigoid diseases.

4.3. Therapy of pemphigoid gestationis

Treatment of pemphigoid gestationis is influenced by pregnancy and should be secure to the fetus. In general, treatment is based on clinical experience. Disorder is almost always self-limiting, but can be associated with post-partum relapse. The goal of the therapy is to reduce pruritus and block the production of autoantibodies. Topical high-potency corticosteroids are the first-line therapy. Usually, topical corticosteroids are combined with systemic antihistamine which is respectable in pregnancy, e.g., chlorpheniramine or cetirizine. If the topical corticosteroid is ineffective, a systemic corticosteroid at a low-mild dose is recommended, e.g., prednisolone up to 0.25 mg/kg/day, as an initial dose with subsequent reduction based on clinical outcome [90, 99]. Severe cases require a high dose of 0.5–1 mg/kg/day of prednisolone [100]. Small and moderate doses of systemic corticosteroid do not affect pregnancy and the fetus, whereas placental enzyme inactivates 88% of prednisolone [101]. The initial dose should continue for 1–2 weeks after disease control is reached, then gradually tapered to an adequate maintenance dose. Alternate day therapy is preferred [102]. Discontinuation of prednisolone therapy depends on the clinical outcome and can be realized after or before delivery. In addition, prednisolone is excreted in breast milk in small amount. A dose up to 40 mg/day is regarded as safe [101]. Severe disease can be treated with intravenous immunoglobulin in a conventional dose. The safety profiles of intravenous immunoglobulin in pregnant women were confirmed by several clinical studies in pregnant women with pemphigus [38, 62]. Another choice of treating severe disease and unresponsive disease to conventional treatment is immunoadsorption [70]. One case report referred to a pregnant patient with severe pemphigoid gestationis who was successfully treated with immunoadsorption followed by systemic corticosteroids. After three procedures, disease control was achieved and pathogenic autoantibodies declined by 89% [103]. Immunoadsorption was evaluated as an effective and safe treatment modality in pemphigoid gestationis.

4.3.1. Therapy of linear IgA dermatosis

IgA dermatosis is a rare diagnosis that can affect adults, especially women of fertile age and children. Treatment should be started with topical high-potency corticosteroids. If topical therapy is ineffective, a systemic corticosteroid should be started, e.g., prednisolone in a dose of 0.25–0.5 mg/kg/day. In severe cases, when corticosteroids do not achieve disease control, prednisolone should be combined with dapsone 1 mg/kg/day. It is recommended to initiate the treatment with dapsone 0.5 mg/kg/day to avoid adverse effects, e.g., hemolytic anemia. According to the clinical outcome, initial therapy can be enhanced up to a conventional dose of 100 mg/day or up to ≤1.5 mg/kg/day. In children, dapsone 0.5–2 mg/kg/day is utilized [89]. Another treatment option is tetracycline (2 g/day) combined with nicotinamide (1.5–2 g/day) [104]. A gluten-free diet is ineffective.

4.3.2. Therapy of mucous membrane pemphigoid (cicatricial pemphigoid)

Treatment of mucous membrane pemphigoid is usually very difficult because of the sequela that may result in blindness and esophageal stricture despite utilization of immunosuppressive medications. The therapy regimen is based on whether ocular mucosa is afflicted or not.

Mucous membrane pemphigoid without ocular involvement requires systemic corticosteroids, e.g., prednisolone over 1 mg/kg/day combined with first-line adjuvant agents like dapsone, azathioprine or mycophenolate mofetil [105]. All immunosuppressive agents are used in conventional doses. The preferred medication in mild disease is dapsone being effective in 30–70% of patients. Response to dapsone can be expected within 2–12 weeks [89]. Mucous membrane pemphigoid with ocular involvement has more severe outcome of disease. In mild-to-moderate ocular mucous membrane pemphigoid, dapsone is recommended at a dose of 50 mg/day up to a maximum dose of 200 mg/day. Another choice, especially if dapsone cannot be used, is to utilize sulfapyridine (500 mg/day or two times daily), or sulfasalazine (1–4 g/day). The anti-inflammatory activity of the last three medications is used in the therapy regimen [106]. A retrospective study of 23 patients with mucous membrane pemphigoid with ocular involvement referred to the good efficacy of mycophenolate mofetil. Control of conjunctival inflammation was achieved in 69.6% of patients within 6 months and in 82.6% of patients within 12 months of therapy [107]. In patients with ocular involvement, another choice is a low dose methotrexate. A retrospective clinical study of 17 patients with mucous membrane pemphigoid demonstrated an improvement in ocular inflammation in 72% of afflicted eyes and improvement of visual acuity in 85% of eyes [108]. Progressive disease in ocular involvement requires a more aggressive therapy regimen. Systemic corticosteroid (prednisolone 1 mg/kg/day) with second-line adjuvant agent, like cyclophosphamide (1–2 mg/kg/d), is recommended. A retrospective study of 94 patients documented the good efficacy of cyclophosphamide combined with prednisolone, resulting in total remission of conjunctival inflammation in 82.9% of patients within 1 year [109]. Recently, new strategies have been employed to treat a severe refractory disease. Small series documented the good efficacy and tolerability of intravenous immunoglobulin. Ten patients with progressive ocular involvement in mucous membrane pemphigoid who were unresponsive to conventional immunosuppressive therapy reported good efficacy and tolerability of intravenous immunoglobulin after receiving 4–12 cycles. Clinical improvement and stabilization of ocular disease was achieved in all patients [110]. Another choice is rituximab. One retrospective study documented the efficacy of rituximab to 61 eyes of 32 patients with ocular involvement in mucous membrane pemphigoid. Twenty-six patients achieved clinical remission with an absence of progressive ocular scarring and ocular inflammation within ≥2 months (average remission of 24.5 months). The therapy regimen of rituximab was used as a monotherapy (6 patients) or in combination (6 patients), rituximab combined with intravenous immunoglobulin (14 patients) and rituximab combined with intravenous immunoglobulin and other immunosuppressive adjuvant (6 patients). The progression of ocular involvement was controlled and no cicatrization developed in the follow-up. Adverse effects were mild and transient [111].

4.3.3. Therapy of epidermolysis bullosa acquisita

It is very difficult to treat epidermolysis bullosa acquisita, especially the classic mechano-bullous form associated with high skin fragility at trauma-prone areas. This form is associated with dystrophic changes, digital contracture and esophageal stricture. Inflammatory epidermolysis bullosa acquisita resembles other autoimmune bullous diseases with responses to anti-inflammatory and immunosuppressive medications. The main stay therapy is systemic

corticosteroids, prednisolone 1–1.5 mg/kg/day. Adjuvant agents with corticosteroid-sparing effect used to treat other autoimmune bullous disease are also effective in the management of epidermolysis bullosa acquisita. Such adjuvants include azathioprine (1–2 mg/kg/day), mycophenolate mofetil (1–2 g/day), methotrexate (7.5 mg/week), and cyclophosphamide (500 mg /day in mode of pulse therapy). In small series, anti-inflammatory drugs including dapsone (25–100 mg/day) and colchicine (0.6–1.2 mg/day) induced remission [112]. Colchicine can be used as a single or combined with systemic corticosteroid or dapsone. Adverse events of colchicine include diarrhea, and renal or hepatic toxicity [113]. One retrospective study of 30 patients with epidermolysis bullosa acquisita referred to the time remission of combined methylprednisolone with mycophenolate mofetil or cyclophosphamide or azathioprine. One year after initiation therapy, complete remission was achieved in 33.3% of patients and partial remission in 32.8% [114]. In severe and refractory cases unresponsive to conventional therapy regimen, intravenous immunoglobulin, rituximab, plasmapheresis, and immunoadsorption could be utilized in conventional doses for autoimmune bullous diseases. All of the therapy modalities were used and documented only in small series of patients with epidermolysis bullosa acquisita, almost always with good efficacy and total or partial remission. In all regimens, a good safety profile was documented. Adverse events did not differ from adverse events in other autoimmune bullous disease [115]. Rituximab combined with intravenous immunoglobulin was referred in 5 patients with refractory epidermolysis bullosa acquisita. Patients received a high number of intravenous immunoglobulin (10–26) and 1–2 cycles of rituximab and achieved adequate improvement of disease, while being well tolerated [116]. The education of patients in the management of topical therapy and preventive measures against common trauma are obligatory.

5. Therapy of dermatitis herpetiformis

The mainstay therapy in dermatitis herpetiformis is a gluten-free diet that ameliorates both skin disease and gluten sensitive enteropathy. Precise maintenance of a gluten-free diet of 2 years cleans the skin disease and heals enteropathy. Adherence to a gluten-free diet should be provided for the whole life. After many years, IgA-antibody deposits disappear from the dermo-epidermal junction in both bowel and skin [6]. The reintroduction of gluten to the diet evokes the recurrence of gluten sensitive enteropathy and cutaneous rash within 12 weeks, frequently sooner. Good adherence to a gluten-free diet within 5–10 years induces improvement of enteropathy and is regarded to have a protective property against lymphoma, which might be associated with dermatitis herpetiformis [117]. Patients on a gluten-free diet must exclude cereals containing gluten and its toxic fractions, including wheat, rye, and barley. Based on some authors, oats can be incorporated into a gluten-free diet, whereas the majority of patients with dermatitis herpetiformis and gluten-sensitive enteropathy can tolerate moderate amounts of pure oats [118, 119]. Furthermore, oats increase the nutrition value of a gluten-free diet. Some studies reported that pure oats do not induce systemic or mucosal antibody response in patients with coeliac disease [119, 120]. However, oats can be contaminated with prolamines from other cereals and pure oats are difficult to prepare. This issue requires further investigation and new agricultural processing and manufacture of oats. Long-term

administration of a gluten-free diet could permit the discontinuation of systemic medication, meaning self-sustaining treatment in dermatitis herpetiformis.

The mainstay medication in dermatitis herpetiformis is dapsone at a dose of 50–150 mg/day. Dapsone usually has a rapid and dramatic effect in suppressing skin symptoms within a few days, but does not have a curable effect on the underlying enteropathy. The effectiveness of dapsone has not been confirmed by clinical studies. Multiple and long-lasting empirical utilization of dapsone in practice confirmed its efficacy and safety in dermatitis herpetiformis.

Another choice to treat dermatitis herpetiformis is sulfonamides, when dapsone fails to control the disease or is not tolerated. Three sulfonamides may be an alternative to dapsone: sulfapyridine (1.5 g/day), sulfamethoxypyridazine (0.25–1.5 g/day), and sulfasalazine (1–2 g/day) [6]. Several case reports referred to an alternative treatment using sulfasalazine, which is commonly utilized in the long-term management of inflammatory bowel disease and as a second-line agent in rheumatoid arthritis and psoriatic arthritis [121]. All three sulfonamides may cause the same adverse events, including hypersensitivity reactions and bone marrow toxicity, resulting in agranulocytosis, aplastic anemia, and methemoglobinemia. More common and not severe adverse effects are nausea, anorexia, and vomiting. Gastro-enteric events could be avoided with administration of an enteric-coated form of medication.

Systemic corticosteroids are not recommended for treating dermatitis herpetiformis, because they are not effective. On the other hand, topical corticosteroids, especially of high potency (e.g., clobetasol propionate) may reduce itching. Another choice to ameliorate pruritus is third-generation antihistamine with specific activity on eosinophil activity.

6. Local therapy in autoimmune bullous diseases

In autoimmune bullous disease, the local therapy is important to prevent infection, to control reepithelization of denuded areas, and to ameliorate pain. Management of bullae depends on their size. Small bullae stay intact and large bullae should be punctured, but the covering should stay at the site of previous bullae. The released roof of blister built up a protective covering that shield the denuded area from secondary infection as well as loss of serum contents. In extensive disease, bathing with antiseptic agent should be applied, e.g., potassium permanganate (1:10,000), chlorhexidine or other commercial agent. Denuded areas should be covered with antiseptic or antibiotic agent in the form of lotions, sprays or cream. A potent topical corticosteroid, e.g., 0.05% clobetasone propionate cream, is preferably used in bullous pemphigoid and can be the self-sustaining therapy in mild bullous pemphigoid [82]. The advantage of topical corticosteroids is their local anti-inflammatory and immunosuppressive activity, which may be helpful in dropping of the systemic corticosteroid. Topical corticosteroids are also successfully utilized to treat minor forms of pemphigus or in the maintenance phase of therapy management [122]. One clinical study demonstrated the good efficacy of clometasone propionate 0.05% cream applied to afflicted areas on skin and mucosa in 7 patients with pemphigus vulgaris and pemphigus foliaceus. Topical corticosteroid was used as self-sustaining therapy. Another topical corticosteroid, betamethasone valerate 0.1% cream,

was applied to the face. The creams were used twice daily for at least 15 days, up to remission. Moreover, when clinical improvement was achieved, topical creams were applied in tapering mode to the area of previous lesions. In 4 patients, relapses occurred when topical treatment was discontinued, but were successfully controlled by reapplication of topical corticosteroid. In 3 patients, topical therapy failed, and a systemic corticosteroid was utilized and combined with other adjuvant agents (dapsone or methotrexate). Topical treatment did not influence anti-Dsg IgG autoantibody titer. No serious side effect was noticed [123]. Topical corticosteroids seem to have only postponed activity in autoimmune bullous disease, because they do not influence the production of pathogenic autoantibody and utilize only anti-inflammatory activity. However, topical corticosteroids may help bypass the period before the systemic immunosuppressive drug should be used to control disease. In addition, minor disease can be controlled by self-sustained topical corticosteroid. Moreover, the monitoring of pathogenic autoantibody may indicate a relative threat of relapse and utilization of systemic medication. In mild disease, a combination of topical corticosteroid with systemic immunosuppressive agent may induce improvement of clinical outcome. In addition, topical corticosteroids may support the systemic agent and advocate healing through their local anti-inflammatory activity. A topical corticosteroid agent can be combined with antibiotic, e.g., gentamycin having dual activity, anti-inflammatory, and antibacterial.

The therapeutic challenge is the pathologic lesions in mucosa, especially in the oral cavity. The response to conventional therapy in oral mucosa occurs in a special environment resulting in delayed healing compared with skin lesions. Topical administration in mucosa should be modified because the saliva dilutes and shortens the therapeutic activity of medication. Therefore, corticosteroid should be implicated into an adhesive paste, which allows longer persistence and activity of the medication. Fluocinonide 0.05%, clobetasol 0.05%, and halobetasol 0.05% ointments compounded 1:1 with Orabase have shown good efficacy in oral management in 12 patients with oral pemphigus vulgaris. The only adverse effect was candida infection in the oral cavity, which afflicted most of the patients [124].

Another option in topical management of the oral cavity is triamcinolone acetonide, a high potency corticosteroid administered perilesional or intralesional to treat recalcitrant and remnant lesions. One clinical study compared perilesional or intralesional triamcinolone acetonide application and topical cream of 0.1% in 35 patients with recalcitrant oropharyngeal pemphigus vulgaris. Perilesional or intralesional triamcinolone displayed a better clinical outcome than topical application and induced complete clinical remission, while reducing the total amount of corticosteroids [125]. A perilesional or intralesional corticosteroid is recommended only in the maintenance phase of therapy, when 4–6 oropharyngeal sites are involved and do not respond to conventional immunosuppressive therapy. In addition, immediate use can be recommended to treat new lesions appearing in the maintenance phase. This regimen is not recommended upon relapse of disease, because the first step is to enhance systemic immunosuppressive medication. Good and meticulous personal oral hygiene and periodic professional oral hygiene sessions are advisable. Topical antiseptic mouthwash solution containing anesthetic agent is useful. However, afflicted mucosa especially that of the oral cavity, shows a refractory clinical outcome and slow response to systemic therapy. Perilesional or intralesional triamcinolone acetonide may improve vegetative tissue formation, especially in intertriginous location in pemphigus vegetans [126].

The topical immunomodulatory agents, calcineurin inhibitors, are new choice in local management of autoimmune bullous disease that promote healing and may enhance reepithelization. A double-blind, placebo-controlled clinical study referred to the good efficacy and safety profile of pimecrolimus 1% cream for cutaneous lesions in 11 patients with pemphigus vulgaris [127]. Another new topical agent, epidermal growth factor (10 μg in cream) was evaluated in a double-blind, randomized, controlled clinical trial and showed accelerating efficacy and a good safety profile in 20 patients with cutaneous lesions of pemphigus vulgaris [128]. Nicotinamide gel 4%, an adjunctive topical gel, was referred as an effective new treatment modality for cutaneous lesions of pemphigus vulgaris in 8 patients in a double-blind, placebo-controlled study [129]. All new topical medications should be confirmed in large clinical studies and eventually in practice.

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