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PEMPHIGUS VULGARIS, CURRENT STATUS AND PROSPECTS

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ვულგარული პემფიგუსი, მიმდინარე მდგომარეობა და პერსპექტივები

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რეზიუმე

ვულგარული პემფიგუსი აუტოიმუნური დაავადებაა, რომელიც ხასიათდება ლორწოვანი გარსებისა და კანის ბუშტოვანი და ეროზიული ელემენტების განვითარებით. ეტიოპათოგენეზი არ არის ცნობილი, თუმცა მკლევარები მიიჩნევენ, რომ გენეტიკური და გარემოს მავნე ფაქტორები შესაძლოა მოქმედებდნენ დაავადების მიმდინარეობაზე.

სტატიაში წარმოდგენილია ვულგარული პემფიგუსის მკურნალობის სხვადასხვა მეთოდი, თავისი დადებითი და უარყოფითი მხარეებით. მნიშვნელოვანია, რომ ყოველი მეთოდი და დოზირება სწორად შეირჩეს, რათა დადებითი თერაპიული ეფექტი მიღწეულ იქნას მინიმალური გვერდითი ეფექტების ფონზე.

Pemphigus vulgaris refers to a group of autoimmune blistering diseases of skin and mucous membranes that are characterized histologically by intraepidermal blisters due to acantholysis (i.e., separation of epidermal cells from each other) and immunopathologically by in vivo bound and circulating immunoglobulin directed against desmogleins 3 and 1. Desmogleins are the desmosomal protein members belonging to the cadherin family. These proteins help the keratinocytes in the epidermis attach to each other. When these proteins are targeted, intraepidermal blisters form usually just above the basal layer [13,14].

Patients will have ongoing, painful, superficial blisters or erosions of the skin and/or mucosa. Some patients will only have mucosal involvement, usually the oral cavity.

Because the blister is forming in the epidermis, it is flaccid and easily ruptured. Many patients will only have crusted erosions where the blisters used to be. The blisters and erosions are painful. The mucosal involvement is usually the oral cavity, but may involve the pharynx, larynx, esophagus, conjunctiva, and genitals. The skin rash typically involves the head, upper trunk, and intertriginous zones. When the patient has ongoing activity of the disease, a positive Nikolsky sign may be present at the edge of a blister. A Nikolsky sign is positive when the top layers of the skin slip away from the lower layers when rubbed, leaving a moist base [7,8].

The four major types of pemphigus include **pemphigus vulgaris**, **pemphigus foliaceus**, **IgA pemphigus**, and **paraneoplastic pemphigus**. Pemphigus vulgaris is the most common form of pemphigus and occurs all over the world. Its frequency is influenced by geographic location and ethnicity. Pemphigus vulgaris occurs between 0.1 and 2.7 per 100,000 people per year. Studies have found certain populations (e.g., people of Jewish ancestry, particularly Ashkenazi Jews, and inhabitants of India, Southeast Europe, and the Middle East) are at a greater risk for pemphigus vulgaris. In some places (e.g., North Africa, Turkey, and South America), pemphigus foliaceous is more common than pemphigus vulgaris [5,6].

Moreover, hereditary associations have been seldom reported in the literature and may be relevant to specific populations; the association with certain HLA haplotypes and alleles has been reported in Brazilian subjects with pemphigus and in family studies conducted in Brazil and in Italy. Such genetic associations hint at a possible genetic predisposition that may underlie susceptibility to PV and to other autoimmune disorders.

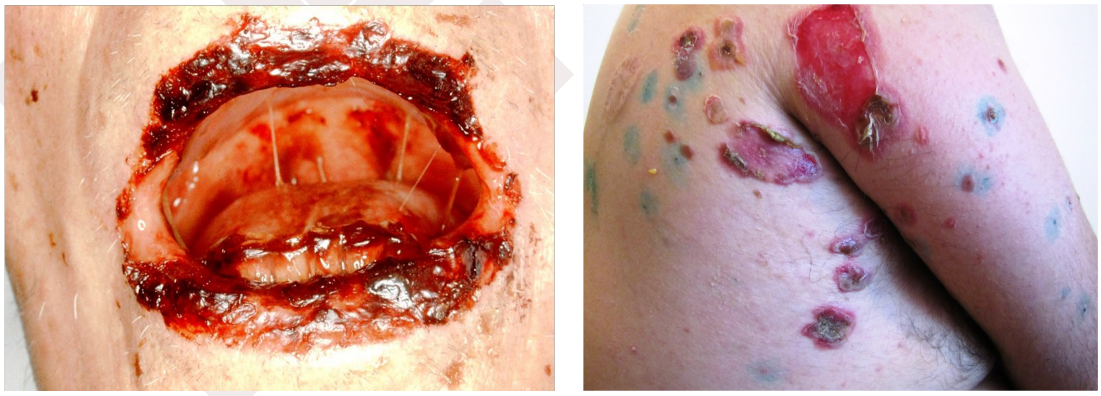
Typically, pemphigus vulgaris and nonendemic pemphigus foliaceous typically occur in adults between 40-60 years old. Pemphigus is pretty rare in children (except for endemic pemphigus foliaceous, which affects children and young adults in endemic areas). Neonatal pemphigus is a rare form of pemphigus that happens when an affected mother's autoantibodies are transferred to the fetus [3].

Like other autoimmune diseases, what causes the pemphigus diseases is not really understood. Researchers believe genetic and environmental factors may influence the diseases. Some suggest that ultraviolet radiation could lead to pemphigus foliaceous and pemphigus vulgaris activity. Pemphigus has even developed following burns or electrical injury. Others have suggested viral infections, certain food compounds, ionizing radiation, and pesticides may trigger or worsen the disease [13,14].

Although there are sporadic case reports of pemphigus associated with the use of several different drugs, the association with penicillamine, and perhaps captopril, is the most significant. The prevalence of pemphigus in penicillamine users is estimated to be approximately 7%. PF (including pemphigus erythematosus) is more common than PV in these penicillamine-treated patients, although either may occur. Both penicillamine and captopril contain sulfhydryl groups that are postulated to interact with the sulfhydryl groups in desmoglein 1, 3, or both, thereby causing pemphigus either by directly interfering with these adhesion molecules or, more likely, by modifying them so that they become more antigenic. The use of these drugs may also lead to a more generalized dysregulation of the immune response, allowing production of other autoantibodies such as those resulting in myasthenia gravis. Most, but not all, patients with drug-induced pemphigus go into remission after they stop taking the offending drug [7,8].

Interestingly, anecdotal case reports have reported improvement of PV with cigarette smoking, as well as with the cholinergic agonists pyridostigmine, carbachol, and pilocarpine. Studies suggest that activation of cholinergic receptors may regulate signaling pathways modulated by PV IgG, thereby affecting cell adhesion. These results are intriguing given the clinical benefit of nicotine noted in other inflammatory diseases, such as ulcerative colitis.

CLINICAL MANIFESTATION. Almost all pemphigus vulgaris patients will have some mucosal involvement. The mouth is the most common location of mucosal lesions, and often is the first area the disease manifests. Other mucous membranes areas are also often affected (e.g., eyes, nose, esophagus, vulva, vagina, cervix and anus). Oropharyngeal erosions can be so painful that the patient is unable to eat or drink. The inability to eat or drink adequately may require inpatient hospitalization for disease control and intravenous fluid and nutrient repletion. (Picture 1.)



Picture 1. Clinical Manifestations.

In women with cervical involvement, pemphigus vulgaris may be mistaken for cervical dysplasia during Papanicolaou (Pap) smears. Because mucosal blisters erode quickly, erosions are often the only clinical findings. The inner mouth (cheeks, lips, and floor of the mouth) are the most common areas for oral lesions.

In the majority of patients, painful mucous membrane erosions are the presenting sign of PV and may be the only sign for an average of 5 months before skin lesions develop. However, the presenting symptoms may vary; in a study from Croatia, painful oral lesions were the presenting symptom in 32% of patients. Most of these patients progressed to a more generalized eruption in 5 months to 1 year; however, some had oral lesions for more than 5 years before generalization. On the other hand, in Tehran, 62% of

patients presented with oral lesions only. Skin involvement without mucous membrane involvement in PV is less common, accounting in one study for 11% of PV cases.

Skin involvement is characterized by soft blisters occurred on normal or reddened, irritated skin. The blisters pop easily, resulting in painful sores that bleed. While any area of the skin may be affected, the palms and soles are usually not.

Blistering may be accompanied by severe pain, itching, burning, and stinging. If extensive, blistering can lead to life-threatening fluid loss, infection, and disfigurement. PV can also cause significant damage to the skin, including nail loss and pigmentary alteration, making timeliness of intervention and treatment essential to prevention of disability. Exposure to ultraviolet radiation may exacerbate disease activity [11,12].

A characteristic finding in pemphigus patients is that erosions can be extended into visibly normal skin by pulling the remnant of the blister wall or rubbing at the periphery of active lesions; additionally, erosions can be induced in normal-appearing skin distant from active lesions by pressure or mechanical shear force. This phenomenon is known as the *Nikolsky sign*. This sign helps differentiate pemphigus from other blistering diseases of the skin such as pemphigoid; however, similar findings can also be elicited in staphylococcal scalded skin syndrome, Stevens– Johnson syndrome, and toxic epidermal necrolysis [4].

PEMPHIGUS SUBTYPES

- Pemphigus vulgaris
- Pemphigus vegetans
- Pemphigus foliaceus
- Pemphigus erythematosus
- Endemic pemphigus foliaceus (e.g., fogo selvagem)
- Immunoglobulin A (IgA) pemphigus
- Subcorneal pustular dermatosis
- Intraepidermal neutrophilic dermatosis
- Paraneoplastic pemphigus

INTRAEPIDERMAL BLISTERING DISEASES WITHOUT AUTOANTIBODIES

- Familial benign pemphigus (Hailey–Hailey disease)
- Bullous impetigo, staphylococcal scalded-skin syndrome
- Blisters from herpes simplex and zoster
- Allergic contact dermatitis (e.g., rhus dermatitis)
- Epidermolysis bullosa simplex
- Incontinentia pigmenti

MOUTH ULCERS/EROSION WITHOUT AUTOANTIBODIES

- Aphthous ulcers
- Candidiasis
- Lichen planus
- Behçet disease

SUBEPIDERMAL BLISTERING DISEASES WITH AUTOANTIBODIES

- Bullous pemphigoid
- Herpes gestationis
- Cicatricial pemphigoid
- Epidermolysis bullosa acquisita
- Linear IgA disease and chronic bullous disease of childhood
- Dermatitis herpetiformis
- Bullous lupus erythematosus

SUBEPIDERMAL BLISTERING DISEASES WITHOUT AUTOANTIBODIES

- Erythema multiforme
- Toxic epidermal necrolysis
- Porphyria
- Junctional or dystrophic epidermolysis bullosa

LABORATORY TESTS. Diagnosis of pemphigus relies on skin biopsy of a fresh lesion for histology to determine the site of blister formation. A skin biopsy of the edge of a blister or erosion will show suprabasilar bulla with acantholysis and minimal inflammation. A skin biopsy for direct immunofluorescence of normal skin next to a blister or erosion will show intercellular IgG and C3. Indirect immunofluorescence of the blood will show intercellular IgG deposition on stratified squamous epithelium. The titer level will usually parallel disease activity. ELISA for desmogleins 3 and 1 are available and may also parallel disease activity. The key diagnostic findings of pemphigus are flaccid bullae with a positive Nikolsky sign.

TREATMENT METHODS. There are Three Phases of Blistering Disease Treatment:

1. *Control:* A period of intense therapy given to suppress disease activity until no new lesions appear.
2. *Consolidation:* Drugs and doses are maintained until complete clearance of lesions.
3. *Maintenance:* Medications can be gradually tapered aiming for the lowest dose that prevent new lesions from appearing.

Initial therapy: control and consolidation. Initial therapy is determined by the extent and rate of the progression of lesions. The priority is to control lesions. Usually in a slow progressive form of the disease, initial treatment includes intralesional injections of corticosteroids or topical application of corticosteroids.

Maintenance therapy. Once most lesions have healed, the dose and type of medication are gradually reduced to limit the risk of side effects. Understanding the rate of dose reduction is determined by clinical response and overall disease activity. It is important to monitor this balance and limit use of unnecessary medication as many fatalities are related to complications with therapy.

Relapse may occur at any time, resulting in renewed disease control effort.

TYPES OF THERAPIES.

SYSTEMIC CORTICOSTEROIDS are the most established therapy for the management of PV. In most cases, when used in high doses, they can rapidly control disease. The most common corticosteroids include Prednisone and Prednisolone. Prednisone suppresses the immune system and limits inflammation in the body. Prednisolone is an oral corticosteroid that is usually used in combination with an immunosuppressant.

Before adjuvant immunosuppressive therapy was available, very high initial doses of prednisone (>2.0 mg/kg/day) were used for treatment, although such regimens have retrospectively been associated with significant morbidity and mortality from therapy. In many patients the disease can be brought under control with a 0.5-1.0 mg/kg/day single daily dose, especially if used in combination with adjunctive immunosuppressive therapy, which is thought to result in fewer complications and decreased mortality as compared to higher dose glucocorticoid regimens. For patients who do not initially respond or worsen, splitting the dose using a twice or three times daily schedule may achieve disease control. The full systemic dose of glucocorticoids has been defined in the consensus guidelines as 1.5 mg/kg/day of prednisone equivalent for 3 weeks. Therefore, patients whose total daily prednisone dose exceeds approximately 100 mg should be considered for adjunctive treatments, discussed below. Some experts still recommend controlling initial refractive disease with escalating doses of prednisone (increasing by 50% every 1 to 2 weeks until disease control or prohibitive side effects occur), with total daily doses as high as 240 mg [18].

Once disease activity is controlled, tapering prednisone to as low a dose as possible should be the goal. Minimal therapy is defined as 10 mg daily of prednisone equivalent. Although there are no set guidelines, if disease activity can be fully controlled on minimal dose prednisone or lower, then glucocorticoid mono-therapy may be feasible depending on the patient's other comorbidities and contraindications to alternative immunosuppressive agents. If patients have continued relapses with daily prednisone doses of 10 mg or higher, adjunctive immunosuppressive agents should be considered.

Interestingly, prednisone can control blistering within days, at a time when the autoantibody titer would be unchanged. A possible explanation is that prednisone may increase the synthesis of desmogleins or other cell adhesion molecules or change their posttranscriptional processing to prolong their half-life. If pemphigus IgG depletes desmosomes of desmogleins, then prednisone could counteract this effect.

Topical steroids can be used for the treatment of pemphigus. To address oral erosion, steroid mouthwash, paste, ointment or aerosol can be used. Topical cyclosporine can also be used for the treatment of oral pemphigus lesions.

If only the mouth and nose are impacted, treatment should be limited to topical steroids, intralesional steroid injections, or occasional short burst of oral corticosteroids. If the gums are involved, topical therapy should be applied with flexible dental trays.

Potential side effects of Corticosteroids may include: headaches, nausea, stomach aches, high blood pressure, stroke, emotional difficulties or mood swings, weight gain. A common side effect of prednisone is Type 2 Diabetes (steroid-induced diabetes), this creates a need for a modified diet. Generally, this type of diabetes will diminish as the dosage of prednisone is reduced and will no longer be present when prednisone is discontinued.

Weight gain is another commonly reported side effect of prednisone. A high protein, low carbohydrate, low fat diet, and a regular exercise program is recommended for those taking prednisone. Osteoporosis glaucoma, and cataracts are also known side effects of prednisone [9,10].

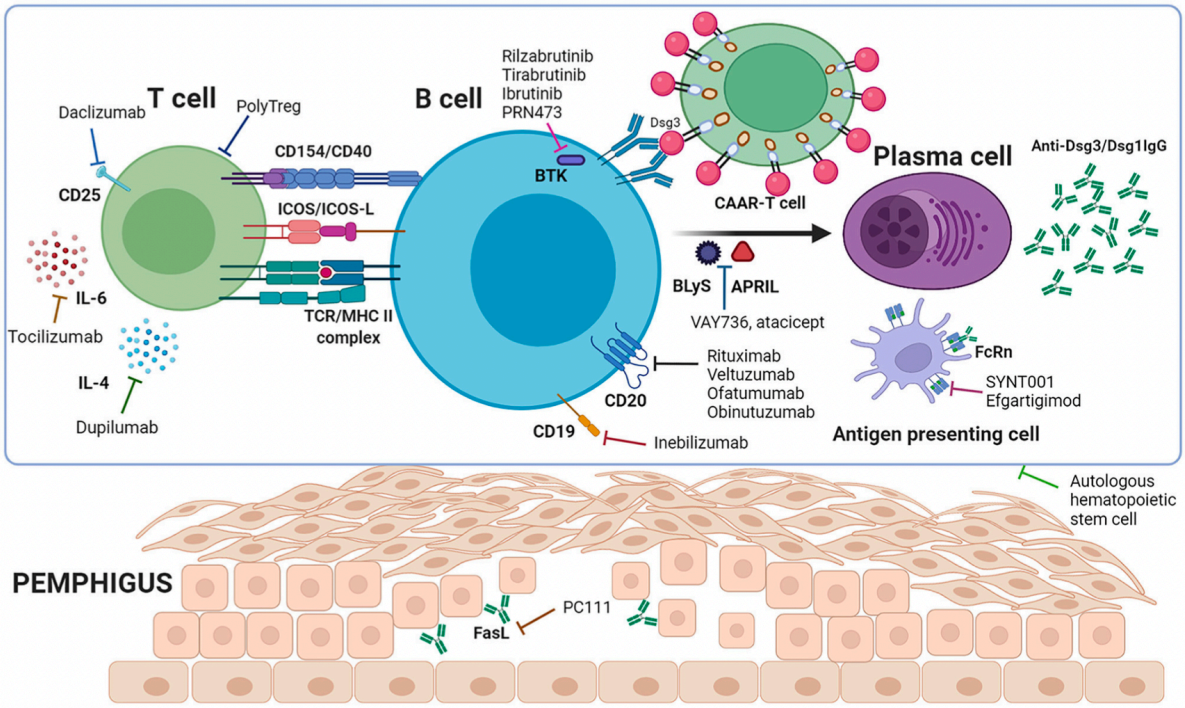


FIGURE 1 | Immune mechanism of pemphigus and targeted therapeutic agents. T cells interact with B cells to provide co-stimulatory signals through CD154/CD40, ICOS/ICOS-L etc., leading to B cell activation, proliferation, and differentiation to plasma cells, and secretion of anti-Dsg3/Dsg1 autoantibodies. Binding of the antibodies to the target antigen among acanthocytes leads to the separation of keratinocytes and intraepidermal blister formation. Rituximab, veltuzumab, ofatumumab, obinutuzumab and inebilizumab deplete autoreactive B cells to prevent their differentiation to plasma cells. PolyTregs, daclizumab, tocilizumab and dupilumab act on T cells, while rilzabrutinib, tirabrutinib, ibrutinib, PRN473, VAY736 and atacicept target B cells, resulting in less activation of autoreactive B cells. CAAR-T cells work to eliminate Dsg3-specific B cells. SYNT001 and efgartigimod saturate FcRn to shorten the half-life of pathogenic IgG autoantibodies. Autologous hematopoietic stem cells function by eliminating autoreactive lymphocytes and re-establishing the immune system (Created with BioRender.com).

IMMUNOSUPPRESSANTS. When greater than minimal doses of glucocorticoids are required for disease control, or if there are contraindications to oral glucocorticoids, other immunosuppressive agents are used for pemphigus therapy. In many cases, treatment regimens often begin with an immunosuppressive agent and prednisone simultaneously. Prospective randomized studies have shown that immunosuppressive agents such as mycophenolate mofetil, azathioprine, and cyclophosphamide have a steroid-sparing effect; retrospective studies suggest decreased mortality with use of adjuvants plus steroids compared to steroids alone.

The following immunosuppressants are used to suppress the immune system. **Azathioprine** (Imuran®, Azasan®) is used after initial treatment to manage pemphigus. **Mycophenolate** (CellCept®, Myfortic®) is composed of several penicillium species that is used after initial treatment for pemphigus. **Cyclophosphamide** (Cytoxan®) is an oral cyclophosphamide that is considered an alternative to azathioprine. Due to the potential toxicities, this drug should be reserved for patients who do not respond to other immunosuppressives. **Cyclosporine** Gengraf®, Neoral®, Sandimmune® Capsules, Sandimmune® oral solutions [18].

Because patients may die from complications of therapy, it is important to monitor all patients closely for potential side effects, such as blood count, liver and kidney laboratory abnormalities, gastrointestinal ulcer disease, high blood pressure, diabetes, glaucoma, cataracts, osteoporosis, and infection. The decision to use immunosuppressive agents, particularly in young patients, must also take into account the potential incidence of malignancies that might be associated with the long-term use of these drugs, as well as the risks of infertility (for cyclophosphamide) and teratogenicity (for mycophenolate mofetil, azathioprine, and cyclophosphamide, which are all pregnancy category D) [9,10].

Main Side effects of immunosuppressants: Azathioprine (chest pain, cough or hoarseness, fever or chills, lower back or side pain, painful or difficult urination, pinpoint red spots on the skin, shortness of breath, sore throat, bleeding gums, blood in the urine or stools); **Mycophenolate** (blood in the urine, chest pain or discomfort, cough or hoarseness, fever or chills, increased cough, lower back or side pain, painful or difficult urination, shortness of breath, swelling of the feet or lower legs); **Cyclophosphamide** (more

common: cough or hoarseness, fever or chills, lower back or side pain, missing menstrual periods, painful or difficult urination; With high doses and/or long-term treatment: blood in the urine, dizziness, confusion, or agitation, fast heartbeat, joint pain, shortness of breath, swelling of the feet or lower legs, unusual tiredness or weakness; Less common: black, tarry stools, pinpoint red spots on the skin; unusual bleeding or bruising)

Azathioprine has historically been considered as a first-line immunosuppressive agent for pemphigus, with clinical remission rates of approximately 50% in retrospective studies. In a prospective randomized trial of high dose methylprednisolone (2.0 mg/kg/day) plus azathioprine (2.0 mg/ kg/day), 72% of patients achieved clinical remission within a mean of 74 days, although 33% experienced significant adverse effects of therapy, including hyperglycemia, dizziness, abnormal liver enzyme tests, and infection [9].

Azathioprine is a prodrug, which is converted to active mercaptopurine, thioguanine, and thioinosine metabolites, in part by thiopurine methyltransferase (TPMT), an enzyme whose levels can vary widely in the population. 89% of Caucasians demonstrate normal to high levels of TPMT, 11% are intermediate, and 0.3% are deficient for TPMT, the latter group representing those who do not tolerate azathioprine therapy. Additionally, 1%-2% of Caucasians may have "super high" levels of TPMT, which is correlated with both treatment resistance as well as increased hepatotoxicity from excessive metabolite production. Altogether, it is estimated that 5% of patients will be azathioprine intolerant, although the genotype-phenotype correlation is imperfect. In patients with normal TPMT levels, the consensus dosing regimen that defines treatment failure is 2.5 mg/kg/day for 12 weeks. From a practical standpoint however, not all laboratories offer TPMT testing. Additionally, since patients with normal levels of TPMT may also experience azathioprine toxicity, it is reasonable to start all patients at a lower dose (e.g., 50-100 mg daily) and titrate upward until clinical remission, the target dose of 2.5 mg/kg/day, or unacceptable side effects result. Frequent blood and liver monitoring should continue, particularly over the first 8-12 weeks when delayed toxicity from the accumulation of metabolites may emerge [18].

Mycophenolate mofetil is also considered to be a first-line immunosuppressive agent for pemphigus. In 2006, the FDA granted orphan drug status to mycophenolate mofetil for the treatment of PV, thereby increasing the feasibility of a new drug approval. Typical doses range from 30-40 mg/kg/day dosed twice daily (2.0-3.0 g/day), although certain patients such as the elderly may achieve disease control with doses as low as 1.0 g/day.

In case series, mycophenolate mofetil has been shown to have a rapid effect in lowering pemphigus antibody titers and decreasing disease activity, even in patients whose disease is unresponsive to azathioprine. A prospective randomized trial comparing methyprednisolone (2.0 mg/kg/day) with azathioprine (2.0 mg/kg/day) or mycophenolate mofetil (2.0 g/day) in pemphigus patients showed 72% in the azathioprine group and 95% in the mycophenolate mofetil group went in clinical remission in a mean of 74 and 91 days, respectively. 19% of patients experienced significant side effects of mycophenolate mofetil therapy, compared to 33% in the azathioprine group. None of these differences was statistically significant [9].

Another prospective randomized study indicated that azathioprine was significantly more effective than mycophenolate mofetil as a steroid sparing agent, although this study compared a full dose of azathioprine (2.5 mg/kg/day) to a partial dose of mycophenolate mofetil (2.0 g/day). Caution with use of mycophenolate mofetil is warranted, as fatal infection and sepsis occurred in 2%-5% of transplant patients receiving mycophenolate mofetil, and increased risk of infection with or reactivation of cytomegalovirus, herpes zoster, atypical mycobacteria, tuberculosis, and John Cunningham (JC) virus (in progressive multifocal leukoencephalopathy) have been noted in post marketing surveillance. Interestingly, mycophenolate mofetil may offer protection against *Pneumocystis carinii* infection [18].

Cyclophosphamide, although more toxic than azathioprine or mycophenolate mofetil, is thought to be very effective in controlling severe disease, with one report of 19 of 23 patients with pemphigus achieving complete remission in a median time of 8.5 months. A variety of small case series have evaluated different cyclophosphamide regimens for pemphigus, including daily oral therapy (1.1-2.5 mg/kg/day), daily oral therapy (50 mg) with intermittent high-dose intravenous dexamethasone and

cyclophosphamide, and immunoablative intravenous cyclophosphamide. All methods were effective in the short-term, although none were curative. Significant side effects, including hematuria, infection, and transitional cell carcinoma of the bladder, were observed with higher dose regimens, although one study using a lower daily dose of cyclophosphamide (1.1-1.5 mg/kg/day) did not report a significantly different safety profile compared with other immunosuppressive agents. Together with the risk of infertility, cyclophosphamide is not generally considered a first-line agent in the treatment of PV [9].

Cyclosporine is a potent immunosuppressant that can effectively suppress immune responses through inhibition of the phosphatase activity of calcineurin. This leads to the downregulation of several transcription factors, especially the nuclear factor of activated T lymphocytes. Moreover, it reduces matrix metalloproteinase-9 expression and blocks both c-Jun N-terminal kinase (JNK) and the p38 signaling pathways. Therefore, cyclosporine could reversibly suppress both humoral and cellular immunity.

Cyclosporine treatment of 3-5 mg/kg/day is infrequently added to systemic corticosteroids as second-line adjuvant therapy in PV. Current data are insufficient to support cyclosporine use in PV, and it is not recommended by the EDF or BAD guidelines [17].

ADDITIONAL THERAPIES. There are additional therapies that can be used when the more standard treatments, discussed previously, are not effective.

Rituximab is a B-cell antibody treatment option for patients with pemphigus that is being used as first line therapy by many clinicians. In June 2018, the FDA approved Rituxan for the treatment of adults with moderate to severe PV. Earlier in the year, the FDA had granted Priority Review, Breakthrough Therapy Designation, and Orphan Drug Designation to Rituxan for the treatment of PV.

B-cells are responsible for producing antibodies for the body, rituximab works as an immunosuppressant that destroys B-cells of the immune system. A course of rituximab is administered with the hope that it will destroy all the B-cells that make antibodies in pemphigus or pemphigoid are removed. Retreatment with Rituxan may be required, usually at six months or longer after the initial treatment. Side effects of **Rituximab** may include: dizziness, weakness, nausea, light-headedness, itch; Additional symptoms for an individual with a fever may include: chills, muscle pain, sneezing, sore throat, trouble breathing, pain in chest or shoulders. Infusion reactions often occur within the first 24 hours after first rituximab infusion [18].

Rituximab is infused intravenously at a dose of 375 mg/m^2 once weekly for 4 weeks. Alternatively, the rheumatoid arthritis dosing regimen can be used (1,000 mg intravenously on day 1 and day 15). The course can be repeated in approximately 6 months for patients with more refractory disease, although a single cycle of rituximab has been shown to be highly effective, with 86% of patients experiencing complete remission lasting 34 months or greater. Disease activity usually begins to remit within 1–2 months after the course of therapy. Some experts consider rituximab the therapy of choice for severe pemphigus uncontrolled by corticosteroids and azathioprine or mycophenolate mofetil or who have contraindications to corticosteroids. However, fatal infections with rituximab therapy have been observed, including *Pneumocystis* pneumonia, reactivation of hepatitis B, and JC virus infection or reactivation causing progressive multifocal leukoencephalopathy. Although these complications are rare, some experts recommend *Pneumocystis* prophylaxis for 1 year following rituximab infusion [1,2].

Intravenous Immunoglobulin (IVIG) therapy is prepared from extracting the plasma in human blood. IVIG is given intravenously; under the skin via a syringe or catheter. The dosage required is patient-specific. To treat pemphigus, the doses are as high as 2000 mg/kg. Due to the fact that doses are higher, infusions are administered over the course of up to five days. This treatment can become a lifetime commitment or the condition may be resolved and IVIG can be discontinued. IVIG is considered to be safe, and the majority of people tolerate it without problems. The adverse reactions occur only in less than 1% of patients: stroke, deep venous thrombosis, and renal failure with sucrose-containing formulations. Some centers will use IVIG to establish initial control of blistering in severely affected patients because it does not increase risk of infection as much as corticosteroids and immunosuppressants. IVIG has also been used in combination with rituximab, although it is unclear whether the combination is safer or more effective compared to either alone [18].

Anti-inflammatory agents such as **Dapsone** and **Tetracyclines** are used as they also may have a steroid sparing effect in mild to moderate disease, often in patients who are in maintenance phase but corticosteroid-dependent. Dapsone is a first-line treatment in dermatitis herpetiformis, linear IgA disease, and milder cases of pemphigus foliaceus [9].

Dapsone must be started after glucose-6-P-dehydrogenase screening and is administered as 7.5mg/kg/day, up to 200 mg/day.

Tetracycline antibiotics. Tetracycline, Doxycycline and Minocycline have been used by some in glucocorticoid-dependent patients in the maintenance phase of therapy, often with Niacinamide (nicotinamide). It is administered as Tetracycline 2 g/day and Niacinamide 1.5 g/day (in divided doses, or Minocycline 100 mg twice daily) and Niacinamide 1.5 g/day (in divided doses).

Methotrexate is a useful and well-tolerated therapy with considerable steroid-sparing effect in patients with pemphigus vulgaris. It may be considered a first-line adjuvant therapy in the treatment of this difficult disease.

Studies regarding the use of methotrexate in pemphigus vulgaris date back to 1968, but few have quantitatively described a steroid-sparing effect conferred by methotrexate. Retrospective chart review was used to analyze the records of patients with pemphigus vulgaris treated with methotrexate at the New York University Langone Medical Center for at least three consecutive months between 2000 and 2012. Diagnosis was made by tissue biopsy and either direct or indirect immunofluorescence tests and enzyme-linked immunosorbent assay. Improvement in clinical symptoms was observed in 91% of patients. Sixteen patients (70%) were eventually weaned completely off prednisone, with a mean time to discontinuation of 18 months. In total 23% of patients enjoyed a partial steroid-sparing effect, requiring a mean maintenance dose of prednisone of 6.75 mg daily. Two patients (9%) developed possible adverse events requiring cessation of the drug, and one patient received no therapeutic benefit from the drug. All patients were treated with 15 mg MTX per week. In another open prospective study of 18 cases, low-dose methotrexate was shown to be effective for maintenance of clinical remission induced by initial short-term use of potent topical steroids [15,16].

Plasmapheresis is sometimes used for severe pemphigus, or for pemphigus that is unresponsive to a combination of prednisone and immunosuppressive agents. Although one controlled study found it to be ineffective, other studies have found that it both reduces serum levels of pemphigus autoantibodies and controls disease activity. Plasmapheresis plus intravenous pulse therapy with cyclophosphamide has been reported to result in remissions of PV. For maximum effectiveness, it is probably necessary to perform plasmapheresis on patients taking immunosuppressive agents to prevent the antibody-rebound phenomenon that can follow the removal of IgG. Protein A immunoadsorption, which removes IgG selectively from plasma, has also been used.

Intravenous, pulse administration of methylprednisolone, 250-1,000 mg given over approximately 3 hours daily for 4-5 consecutive days, can result in long-term remissions and decrease the total dose of glucocorticoids necessary to control disease. Although the purpose of this therapy is to decrease the incidence of complications of long-term steroid use, it can result in all the usual glucocorticoid complications, as well as cardiac arrhythmias with sudden death, and its use is controversial. Furthermore, a controlled trial found that adjuvant oral dexamethasone pulse therapy in addition to standard therapy with prednisolone and azathioprine for PV is not beneficial. It may be that simply giving divided lower doses of prednisone could accomplish the same result with fewer side effects [9].

ORAL THERAPY.

For multiple oral erosions, corticosteroid mouthwashes are practical, for example, soluble betamethasone sodium phosphate 0.5 mg tablet dissolved in 10 mL water may be used up to four times daily, holding the solution in the mouth for about 5 min. Isolated oral erosions could be treated with application of triamcinolone acetonide 0.1% in adhesive paste or clobetasol 0.05% gel. Topical cyclosporine (100 mg/m1) in oral pemphigus has been described and may be of some benefit but is expensive.

CONCLUSION.

The ultimate goal is to achieve rapid disease control, complete disease remission, and disease cure. With the accumulation of the knowledge of pemphigus pathogenesis, novel targets could be identified, and more therapeutic agents with improved efficacy will be developed and applied for PV management in clinical practice. It is important that all physicians, doctors, and specialists involved with a treatment are in contact with one another to avoid conflicting medications and to be sure that each doctor's treatments are working in harmony. Lab results should also be shared with all physicians. Each individual may experience side effects when they begin a new treatment, it is important to monitor and contact physician if patients experience any adverse reactions.

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PEMPHIGUS VULGARIS, CURRENT STATUS AND PROSPECTS

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SUMMARY

Pemphigus vulgaris refers to a group of autoimmune blistering diseases of skin and mucous membranes. Like other autoimmune diseases, what causes the pemphigus diseases is not really understood. Researchers believe genetic and environmental factors may influence the disease.

The article presents various methods of treatment of pemphigus vulgaris, with its pros and cons. It is important that each method and dosage are properly chosen to achieve a positive therapeutic effect on the background of minimal side effects.

Keywords: Pemphigus vulgaris, treatment, side effects.