International Journal of Science and Research (IJSR)
ISSN: 2319-7064
SJIF (2022): 7.942

Management of Pemphigus: Current Therapeutic Strategies

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Abstract: Pemphigus ***is an IgG-mediated autoimmune disease that causes blistering of the skin and affects oral cavity, nose, throat, eyes, and genitals. Blisters and erosions are the characteristics of the disease which affects stratified squamous epithelium, including the skin and oral mucosa. Blisters and erosions are caused due to acantholysis (loss of cell adhesion). The illness typically progresses slowly and reoccurs, with possible adverse impact on the patients' quality of life. It is majorly subclassified into following types: pemphigus vulgaris, pemphigus foliaceus, paraneoplastic pemphigus. Desmoglein 1 and 3, which are cell-cell adhesion molecules present in desmosomes, are the usual targets of IgG autoantibodies. The diagnosis is made based on clinical symptoms and histological and immunochemical studies are used to confirm it. Systemic corticosteroids are currently the first-line therapy, along with adjuvant therapies such intravenous immunoglobulin, immunosuppressive drugs, and plasmapheresis. As a first line of therapy, azathioprine and mycophenolatemofetil are effective. It has been found that rituximab, an anti-CD20 monoclonal antibody that causes B-cell depletion, improves patient survival. Controlling the condition, preventing relapses, and avoiding side effects linked to the prolonged use of steroids and immunosuppressive agents are the primary goals of managing pemphigus.***

Keywords: Pemphigus, Acantholysis, Plasmapheresis, IgG autoantibodies

1. Introduction

The term pemphigus stems from the Greek ‘pemphix’, which means blister or bubble, and it describes a group of chronic blistering epithelial diseases in which the production of IgG autoantibodies against extracellular domains of cell membrane proteins of keratinocytes results in acantholysis (the loss of cell-cell adhesion between keratinocytes) [(1).] Pemphigus was first described in 1788 by Stephen Dickson, who observed a patient with a blister on her tongue [(2).] Pemphigus can be divided into three major forms: pemphigus vulgaris (PV), pemphigus foliaceus (PF), and paraneoplastic pemphigus (PNP). Autoantibodies directed against Dsg3 and Dsg1 are mainly identified in PV; anti-Dsg1 autoantibodies are the serological hallmark of PF. In addition, autoantibodies targeting non-Dsg antigens have been reported in PV patients, such as IgG against alpha9 acetylcholine receptor, various mitochondrial nicotinic cholinergic receptor subtypes and desmocollins 1-3 [(3).] The primary objective of the therapeutic management of PV is initially to control the disease, heal the bullous skin and mucous lesions, and minimize the associated functional impairment. Subsequently, the real challenge is to prevent relapses in the long run and avoid adverse events associated with the prolonged use of steroids and immunosuppressive agents. Such intent requires close clinical monitoring of efficacy and safety of treatment [(4).]

Pemphigus subtypes:

- Pemphigus Vulgaris-PV presents as multiple flaccid blisters limited to the suprabasal layer in the epidermis or mucosal membrane, whilst the keratinocytes in the top layers maintain their cell cohesion. Interestingly, the basal cells also maintain their adhesion to the basement membrane, thereby histologically appearing like a ’row of tombstone’ [(5).] There are several variants like pemphigus vegetans (PV with fungoid vegetations).
- Pemphigus foliaceus-Acquired form of pemphigus, there is only skin involvement without mucosal lesions, caused by immunoglobulin G (IgG) antibodies directed against desmoglein-1 (Dsg1) found in the granular layer of the epidermis [(6).] Pemphigus erythematosus is the variant.
- Paraneoplastic pemphigus-severe form of pemphigus associated with an underlying tumor associated with non-Hodgkin’s lymphoma, leukemia or thymoma, caused by both humoral and cellular autoimmune responses.
- Drug induced pemphigus-penicillamine, captopril, and tiopronine [(7)]

Etiology and Pathogenesis

1) Genetics

A strong association with pemphigus vulgaris has been observed for HLA-DRB1*0402 (which is predominant in Ashkenazi Jews), HLA-DRB1*1401, HLA-DRB1*1404 and HLA-DQB1*0503 (which are both prevalent in non-Jewish patients of European and Asian descent) [(8).]

The HLA class II loci HLA-DRB1*04 and HLA-DRB1*14 were linked to non-endemic pemphigus foliaceus, and a strong correlation has been found in fogoselvagem with HLADRB1*1402 and HLA-DR*0404 [(1)]

The HLA-DRB1*03 allele confers strong susceptibility to paraneoplastic pemphigus in French Caucasian patients ([(9)]

2) Desmogleins

Desmogleins (Dsgs) are thought to be synthesized as inactive precursor proteins and are cleaved by convertases to yield mature adhesive molecules [(21).] Desmogleins have four isoforms (Dsg 1-4). Dsg1 and Dsg3 are the main adhesion glycoproteins in the stratified squamous epithelia, they are coexpressed, and have a synergic role in the maintenance of epithelial integrity [(15).]

Anti-desmoglein 1 and anti-desmoglein 3 IgG antibodies can be found circulating in serum and bound to the surface of skin and mucosal keratinocytes in patients with pemphigus, even in epithelia that appear normal [1]. Different expression of the pemphigus autoantigens (Dsg1 and Dsg3) in the cornified and non-cornified epithelium, skin and mucosae are differentially affected by anti-DsgIgG autoantibodies [3]. Dsg1 is the autoantigen recognized by PF antibodies, whereas Dsg3 is specifically recognized by PV autoantibodies.

The correlation between autoantibody profile and clinical phenotype can be physiologically explained by the desmoglein compensation theory, which is based on the findings that desmoglein 1 and desmoglein 3 can compensate for each other when they are co-expressed in the same cell and the adhesive function is impaired in one of them [10, 11, 12].

Dsg 3 is expressed throughout the oral mucosa, especially in the upper two-thirds, whereas in the epidermis it is expressed only in the basal and immediate suprabasal layers [13]. Conversely, Dsg1 is expressed throughout the epidermis and oral mucosa but more intensely in the subcorneal layer and very weakly in the deep epidermis [14].

The clinical phenotype of pemphigus is defined by the antidesmoglein autoantibody profile. Some patients with PV have only anti-Dsg3 IgG, whereas other PV patients have both anti-Dsg3 and anti-Dsg1 IgG. Patients with PF have only anti-Dsg1 IgG [15].

3) Blister Formation and Acantholysis-

Ig autoantibodies directed against Dsg antigens lead to epithelial acantholysis presumably through several synergistic mechanisms [3]. Pemphigus autoantibodies are predominantly of the IgG4 subclass, which does not activate complement, poorly activates immune effector cells via its Fc region and does not effectively crosslink antigen. Thus, autoantibody binding can directly compromise desmosomal function [1].

The most important targets for Ig antibodies in pemphigus are extracellular domains of Dsg. Dsg show five extracellular cadherin repeats domains (EC1-EC5); the amino-terminal EC1 and EC2 domains, which play a pivotal role in adhesive interactions, are usually targeted by pemphigus antibodies [3].

Management

Most treatments aim to reduce serum autoantibodies to relieve symptoms, either directly or by suppressing the immune system generally**.** The goal for the initial phase of therapy is disease control, which means preventing the formation of new blisters and starting the healing process of the existing ones. The initial phase ends when no new blisters appear for 2 weeks and most existing lesions have healed (disease control). This moment usually marks a change in the therapeutic regimen and the end of the consolidation phase of therapy [1]

Patients with pemphigus vulgaris and pemphigus foliaceus typically benefit from the same type of treatment but Patients with paraneoplastic pemphigus, however, are notably resistant to the same. Anecdotal evidence supports the use of corticosteroids, cyclophosphamide, plasmapheresis, rituximab, cyclosporine, rituximab plus daclizumab, andalemtuzumab [1]

Systemic Corticosteroids

The first-line treatment during the starting phase of management is corticosteroids, owing to their rapid effect (within days). Even though there is the same level of circulating autoantibodies, corticosteroids can ameliorate illness within days. The rapid therapeutic effect of corticosteroids is attributed to increased transcription of desmogleins and other cell adhesion molecules, which counteracts the autoantibody-induced interference with desmoglein adhesive function [16]. Accordingly, topical and intralesional corticosteroids can be used as adjunctive therapy or even monotherapy in localized mild disease [1].

The guidelines by EDF and European Academy of Dermatology and Venereology recommend initial prednisolone dose at 0.5 mg-1.5 mg/kg/d and if control of the disease is not reached within 2 weeks, a higher prednisolone dose (up to 2 mg/kg) could be administered [18]

Mechanism of action: Corticosteroids have strong anti-inflammatory and immunosuppressive effects. They affect almost every aspect of the immune system. They are potent inhibitors of NFkappa B activation and have effects on leukocyte movement, leukocyte function, and humoral factors. In addition they have inhibitory effects on many known cytokines [17].

CSs can be combined with an immunosuppressive agent, particularly when complications due to expected prolonged use (4 months) such as hypertension, diabetes mellitus, and osteoporosis are expected. In the case of contraindications to glucocorticoids or complications due to expected prolonged use (4 months) consists in the combined or single use of immunosuppressants such as azathioprine, MMF, dapsone, methotrexate, cyclophosphamide, and cyclosporine. (4)

Mycophenolatemofetil

It is considered as first line adjuvant immunosuppressant. It is a steroid sparing agent. MMF is a prodrug that converts to mycophenolic acid (MPA) upon oral administration. MPA downregulates the immune system by selective impairment of inosine monophosphate dehydrogenase, leading to a blockade of the de novo pathway of purine synthesis in T and B cells, affecting both cellular and humoral immunity. Because lymphocytes are mainly dependent on the de novo pathway for purine biosynthesis, lymphocytes are the primary target of MPA [22].

The optimal dose is weight dependent with a dose of 2 g/d recommended for the average patient of 75 kg. Progressive dose increase by 500 mg/wk until the final dose of 2 g/d has been proposed to avoid gastrointestinal adverse events [19]

MMF in combination with prednisolone seems to have a more prominent beneficial role in patients with relapses of PV or in cases of refractory PV who have failed previous

treatments [20, 21]. It is not recommended during pregnancy owing to the risk of teratogenicity [1].

Azathioprine

Azathioprine (AZA) is considered as first line adjuvant immunosuppressant steroid sparing agent. AZA is a prodrug that converts to 6-mercaptopurine after oral administration. AZA down-regulates purine metabolism leading to a block of DNA, RNA and proteins synthesis. Furthermore, AZA inhibits mitosis and leads to immunosuppression in several ways [23]. AZA reduces the number of monocytes and Langerhans cells, decreases γ-globulin production, and lower T-cell as well as suppressor B cell activity. Furthermore, it blocks T-helper-cell dependent responses of B cells [3].

6-mercaptopurine can be inactivated to 6-methyl-mercaptopurine by thiopurinemethyltransferase (TPMT) enzyme [24]. Dose varies between 1 and 3 mg/kg/d, based on the activity of the thiopurinemethyltransferase (TPMT) enzyme. When TPMT levels are high, normal doses of azathioprine (up to 2.5 mg/kg/d) are administered, while adults with PV and intermediate or low TPMT levels should receive a maintenance dose (up to 0.5-1.5 mg/kg/d). Azathioprine should not be used in patients with no TPMT activity [4].

AZA is generally preferred for patients with renal failure, because the active moiety of mycophenolatemofetil, mycophenolic acid, is not cleared by haemodialysis and leads to drug intolerance [25]. AZA can cause potentially life-threatening bone marrow suppression [1]. AZA has been associated with increased risk of lymphoma [26].

Cyclophosphamide

Cyclophosphamide is considered a second-line immunosuppressant adjuvant therapy according to the EDF guidelines. It can be administered either as a 500 mg IV infusion or as 2 mg/kg/d orally [18].

CYP is an alkylating prodrug with antineoplastic and immunosuppressive properties. CYP is converted in the liver into two active metabolites, phosphoramide mustard and aldophosphamide, which downregulate DNA replication and induce cell death. CYP shows also a blocking activity on proliferation, cytokine production, and lymphocyte-induced inflammation [27, 28].

The potential long-term side effects (infertility, increased risk of cancer, infections, genitourinary complications, and lymphopenia) further limit cyclophosphamide's use [29].

Dapsone

Dapsone is used alone or in combination with topical clobetasol as first-line therapy in mild PF. Evaluation of serum glucose-6-phosphate dehydrogenase (G6PD) activity is mandatory before administration [3]. Dapsone is recommended in a dose of 100 mg/d or up to #1.5 mg/kg/d as a steroid-sparing agent [18].

Methotrexate

Methotrexate (MTX) (10-20 mg/week) is considered a third line CS-sparing drug in PV [30]. A recent retrospective study reported that 21 out of 25 patients downgraded PV severity and were able to taper steroids after 6 months when using adjuvant therapy with 15 mg of methotrexate per week [31].

Rituximab

Rituximab is an anti-CD20 monoclonal humanized antibody with the potential to reduce desmoglein autoantibodies and selectively deplete B cells [4]. A multicentre, prospective, randomized trial of rituximab as a first-line therapy for pemphigus was recently published, resulting in designation of rituximab as a US FDA Breakthrough Therapy [1].

According to the EDF, rituximab is recommended for patients who continue to require more than 10 mg of prednisolone in addition to an immunosuppressive adjuvant. Administration schedule in literature is either 1, 000 mg IV every 2 weeks or 375 mg/m2 every week [4]. High-dose rituximab was associated with a longer duration of complete clinical remission than low-dose rituximab (17 and 9 months, respectively) [1].

Mode of action-

RTX is a chimeric type I monoclonal anti CD20 antibody, consisting of a human Fc portion and a murine variable region which serve as CD20 binding site [32]. RTX target, CD20, is a transmembranereceptor that is expressed across various developmental stages of the B-cell, from the pre-B cell to the mature; while, early precursor pro-B cells and antibody-producing plasma cells do not express it [33]. RTX binds near the large extracellular loop of CD20 [34]. RTX binding to CD20 induces B-cell depletion by different mechanisms:

1) direct induction of programmed cell death, which is dependent on activation of caspases and involves intracellular molecules, including Src kinases, p38 MAPK and NFkB [3]
2) complement-dependent cytotoxicity, that happens when C1s binds to RTX opsonized cells and triggers complement activation and formation of the membrane attack complex (MAC), which eventually induces cell lysis [35]
3) antibody-dependent cytotoxicity, which consists of activation of NK cells through binding the human Fc portion of RTX to the FcRIII receptor: this activates NK cells to release cytotoxic mediators, including perforins and granzyme B, which induces caspases-dependent cell death in the target lymphocyte [36]
4) antibody dependent phagocytosis, in which neutrophils, monocytes and macrophages bind RTX opsonized B-cells through the Fcγ Receptor [35]

Resistance to rituximab efficacy - Resistance to rituximab therapy can occur owing to either genetic polymorphisms or the development of human anti-chimeric antibodies against the murine fragment of rituximab that prevent the drug from binding to B cells. In pemphigus, human anti-chimeric antibodies were associated with adverse reactions to rituximab infusions and poor treatment response [37].

Adverse effects-Serious adverse effects can occur during rituximab therapy. In a meta-analysis of 153 patients with pemphigus who received rituximab, infections occurred in 11 (7.2%) patients and 2 (1.3%) cases were fatal;

hypogammaglobulinaemia was observed in 3 (2%) patients [1]. Rituximab does not eliminate the need for steroids or immunosuppressive agents, and most patients in published studies did use such therapy along with rituximab [4].

Intravenous immunoglobulins

IVIg consist of human plasma-derived IgG, sugars, salts and solvents. IVIg derived from large plasma pools [3]. The usual dose is 2 g/kg/cycle IV administered over 2-5 consecutive days, monthly [18]. Immunosuppressive adjuvants and systemic CSs may be combined with IVIG as adjuvant therapy. The main mode of action is an increased catabolism of immunoglobulins via binding to the neonatal Fc receptor (FcRn) [3].

Adverse effects-Immediate adverse effects (occurring within the first hour of infusion) include headache, nausea, fever, tachycardia, malaise, arthralgia, and dyspnoea. Delayed reactions include headache, acute renal failure, thromboembolic events, and pseudohyponatremia [38]. Myocardial infarction, thrombosis, pulmonary embolus and Stevens-Johnson syndrome, have been also described. Thrombosis can be provoked by hypercoagulability due to increased blood viscosity, augmented fibrinogen production, and raised platelet activity [39]. It is not recommended for people who have a complete IgA deficiency.

Infliximab

Infliximab is a chimeric monoclonal antibody against tumor necrosis factor alpha (TNF-α). TNF-α has been found to be strongly expressed by the acantholytic cells in PV [40]. There are several case reports and case series of PV patients successfully treated with infliximab. On the other hand, there are also several case series and a small comparative study showing no benefit in patients with PV treated with infliximab [4].

Other therapeutic strategies

Other therapeutic approaches for PV employed by dermatologists all around world in clinical practice include immunoadsorption, therapeutic plasma exchange, or plasmapheresis, and extracorporeal photochemotherapy**.**

Immunoadsorption

Rapid removal of circulating autoantibodies against Dsg1 and Dsg3 can be achieved by immunoadsorption [4]. When CSs combined with azathioprine or mycophenolate fail to control the disease, it is advised in individuals with refractory PV. Four treatments of immunoadsorption on 4 consecutive days (2.5-fold plasma volume/d), repeated after 4 weeks, if needed, are the recommended schedule [18].

In IA, the blood is passed through adsorber columns, in which molecules with high affinity for IgG, i. g. protein A (Immunosorba R) or the synthetic peptide PGAM146 (Globaffin R), function as a ligand [3]. Although the principles of IA are comparable to plasmapheresis, IA does not remove plasma proteins like albumin and clotting factors.

Patients with pemphigus who had severe and widespread illness at baseline would benefit greatly from IA. Since IA enables the rapid elimination of harmful antibodies, whose serum concentration indicates both the activity and severity of the disease, combining IA with immunosuppressive agents yields faster clinical responses than the immunosuppressive medication alone. Positive gradient between skin and blood leads skin-bound autoantibodies into the systemic circulation due to removal of circulating autoantibodies. To avoid a rebound increase of the autoantibody titer, IA is therefore performed on 3 or 4 consecutive days, and then repeated on a monthly base based on the disease response, autoantibody serum concentrations and treatment tolerability [3].

Contraindications include severe systemic infections, cardiovascular diseases and hemorrhagic diathesis [4]. IA is superior to plasmapheresis but the primary limiting factor is the expensive cost of the adsorbers.

Plasmapheresis

Plasmapheresis is an extracorporeal blood purification technique, in which the blood is continuously removed from the patient and separated into cellular components and plasma; the cellular compartments are returned to the patients along with replacement fluidlike albumin [4]. Plasma exchange has been suggested as an effective adjuvant therapy for reducing disease activity in individuals with severe PV by lowering serum levels of autoantibodies.

There is no standardized protocol for the number and frequency of sessions; however, four or five plasma exchanges, each exchange consisting of 1-1.5 plasma volumes, over a period of 7-10 days constitute an adequate short-term therapy to remove 90% of the total initial body immunoglobulin burden [41].

Double filtration plasmapheresis (DFPP) is a relatively new procedure that, similar to IA, removes selectively immunoglobulins, while minimizing the loss of albumin [3]. Plasma exchange is generally safe, and the danger of infection is primarily brought on by the steroids and immunosuppressive medications that are administered in conjunction with it. Other transient and minor adverse effects of plasma exchange that have been reported include thrombocytopenia, hypogammaglobulinemia, fluid overload leading to hypertension and pulmonary edema, hypoproteinemia, anemia, leucopenia, and hypocalcemia [4].

Extracorporeal photochemotherapy

Extracorporeal photochemotherapy involves the collection of mononuclear cells with a cell separator, their irradiation with ultraviolet-A (UV-A) light in the presence of 8-methoxypsoralen, and reinfusion of the treated cells into the patient [4].

2. Conclusion

CSs continue to be the preferred method of treating PV. Azathioprine and Mycophenolatemofetil are the first line treatment of pemphigus. Rituximab can be beneficial in recalcitrant pemphigus when other treatment modalities show no response. The incidence of adverse events and morbidity has decreased with the introduction of systemic treatment for PV. The degree of evidence and strength of therapeutic recommendations will, however, increase as

more research take into account common definitions and criteria, leading to a shorter course of treatment and an improvement in patients' quality of life.

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