

## REVIEW ARTICLE ON TREATMENT OF PEMPHIGUS VULGARIS

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## ABSTRACT

Pemphigus vulgaris is autoimmune disorder, due to autoantibodies against the desmosomal glycoprotein desmoglein 3 (Dsg3) cause blisters due to loss of keratinocyte cell-cell adhesion, with a mortality rate of approximately 5-15% and corticosteroid, immunosuppressant and biological agents are used as management of PV. The goal of PV therapy is to induce and maintain remission. The current treatment paradigm involves a step-up approach, moving to aggressive, powerful therapies only when milder therapies with fewer potential side effects fail or when patients declare themselves to have an aggressive disease. This review focuses on the current treatments for pemphigus vulgaris.

**Keywords:** Acantholysis, Corticosteroid, Immunosuppressive, IVIG, Plasmapheresis, Rituximab

## INTRODUCTION

Pemphigus vulgaris is an autoimmune disorder that involves blistering and sores (erosions) of the skin and mucous membranes. The term pemphigus refers to a group of autoimmune blistering diseases of the skin and mucous membranes characterized histologically by intraepidermal blister and immunopathologically by the finding of in vivo bound and circulating immunoglobulin G (IgG) antibody directed against the cell surface of keratinocytes. These intercellular or pemphigus vulgaris antibodies bind to keratinocyte desmosomes and to desmosome-free areas of the keratinocyte cell membrane. The binding of autoantibodies results in a loss of cell-to-cell adhesion, a process termed acantholysis. The antibody alone is capable of causing blistering without complement or inflammatory cells here. Pemphigus antibody binds to keratinocyte cell surface the molecules desmoglein 1 and desmoglein 3. The binding of antibody to desmoglein may have a direct effect on desmosomal adherens or may trigger a cellular process that results in acantholysis. Patients with the mucosal form of pemphigus vulgaris have only antidesmoglein 3 autoantibodies. Patients with active disease have circulating and tissue-bound autoantibodies of both the immunoglobulin G1 (IgG1) and immunoglobulin G4 (IgG4) subclasses. More than 80% of the patients with active disease produce autoantibodies to the desmosomal protein desmoglein. pv are treated by mainly corticosteroids, immunosuppressive and anti-inflammatory, biological agent. Among these treatment corticosteroid are preferred in severe case but having more adverse effects. Other agent are developed and investigated for improve efficacy and reduce side effects.

## TREATMENT

## Corticosteroids

Systemic glucocorticoids are the cornerstone of treatment. The advent of corticosteroids in the 1950s was accompanied by a 45% reduction in mortality (Bystryn JC, 1984); however, the long-term, high-dose courses of systemic corticosteroids often used to control pemphigus are associated with significant sequelae. There is no standardized approach to the administration of corticosteroids in pemphigus, although continuous oral administration is the most common. Clinical improvement may be observed within days of starting treatment, although cessation of new blister formation may take 2-3 weeks (Lever WF, 1984; Ratnam KV, Phay KL, Tan CK, 1990; Lapidoth M, David M, Ben-Amitai D et al, 1994) with full healing occurring at 6-8 weeks. (Lever WF, White H, 1963) Glucocorticoids are the mainstay of treatment for most bullous disorders. They have anti-inflammatory and immunosuppressive effects from the inhibition of the production of proinflammatory cytokines. They diminish the number of circulating T-cell lymphocytes and reduce their responsiveness to antigens. In addition, glucocorticoids decrease antibody production. Adverse effects from glucocorticoids

arise both from their long-term use and abrupt discontinuation. Immunosuppression increases patients' risks of developing infections. In addition, prolonged use may lead to osteoporosis, osteonecrosis, cushingoid fat redistribution, and acid reflux disease. Patients may also develop electrolyte imbalances, hyperglycemia, hypertriglyceridemia, proximal myopathy, hyperactivity, glaucoma and cataracts

## Corticosteroid Dosing

In this study, 22 newly diagnosed pemphigus patients were randomized to low-dose (45-60 mg) or high-dose (120-150 mg) prednisolone and followed-up for 5 years. All patients achieved resolution of blister formation and were seronegative for autoantibodies at 3 months. There was no significant difference in the duration of treatment required to achieve initial remission, the number of relapses, the timeframe to relapse, or the incidence of complications between the two groups, indicating that there was no advantage to a high-dose regimen. The optimum CS dosing schedule is not known and dosing schedules are largely empirical and based on practical experience. Early studies advocated high doses, e.g. initial doses of 120-180 mg prednisolone daily (Lever WF, White H, 1963) one study estimated that up to 77% of deaths were CS related. (Rosenberg FR, Sanders S, Nelson CT, 1976) Therefore, a more moderate approach to CS therapy has been advocated. However, only one controlled trial has compared dosing schedules; initial therapy with low-dose prednisolone (45-60 mg day<sup>-1</sup>) was compared with high-dose prednisolone (120-180 mg day<sup>-1</sup>) in patients with severe pemphigus (19 with PV) affecting more than 50% of their body surface. There was no significant difference in the duration to achieve remission and in relapse rates at 5 years, and there were no deaths (Ratnam KV, Phay KL, Tan CK, 1990). A tailored dosing schedule has been advocated according to disease severity and a modified regimen is suggested here. Patients with mild disease are treated with initial prednisolone doses of 40-60 mg day<sup>-1</sup> and in more severe cases, 60-100 mg day<sup>-1</sup>. If there is no response within 5-7 days, the dose should be increased in 50-100% increments until there is disease control. Once remission is induced and maintained with healing of the majority of lesions, the dose of CS can be cautiously tapered. A 50% reduction every 2 weeks has been suggested.<sup>[1]</sup>

## Pulsed Corticosteroid Therapy

Pulse therapy refers to discontinuous intravenous infusion or oral dosing of high-dose glucocorticoids in short bursts. It is based on the rationale that the steroid pulses may cause rapid control of disease and decrease the need for long-term steroid use, thereby reducing the complications of long-term usage. (Toth GG, van de Meer JB, Jonkman, 2002) This has not been conclusively proven to be effective owing to the studies having inadequate power to exclude a beneficial effect because of the very low number of patients studied. The only RCT evaluating the utility of pulse therapy in pemphigus

studied 20 PV patients with new disease activity randomized to oral dexamethasone 300 mg or placebo pulses on 3 consecutive days per month, in addition to conventional treatment. (Mentink LF, Mackenzie MW, Tóth GG et al., 2006). In this study, the cohort receiving the pulse therapy was found to have faster clinical resolution of symptoms, with statistically significant difference.

#### Adjuvant Immunosuppressive Therapy

##### Immunosuppressive and anti-inflammatory agent

Adjuvant steroid-sparing therapies have been employed in the management of pemphigus, with the belief that they not only reduce the cumulative glucocorticoid dose, but increase the efficacy of treatment. Common adjuvant therapies utilized include azathioprine, mycophenolatemofetil, cyclophosphamide, ciclosporin, methotrexate, chlorambucil, gold, dapsone, and tetracycline/nicotinamide. These agents typically require 4–12 weeks to demonstrate any therapeutic effect, thus their use is essentially in maintaining remission, rather than inducing it. A recent RCT by Chams-Davatchi et al. of 120 newly diagnosed PV patients compared prednisone monotherapy with prednisone plus adjuvant azathioprine, mycophenolatemofetil or intravenous cyclophosphamide pulse therapy. (Chams-Davatchi C, Esmali N, Daneshpazhooh M et al. 2007) All four regimens induced complete remission in 70–80% patients with no statistically significant difference observed between them in terms of remission or side effects. The authors proposed that azathioprine was the most efficacious steroid-sparing agent, followed by cyclophosphamide, then mycophenolatemofetil, based on the mean cumulative steroid dose between cohorts.

##### Azathioprine

Azathioprine is a purine analog used as a steroid-sparing agent for autoimmune bullous diseases. It is a prodrug, which is converted first to 6-mercaptopurine, then to 6-thioguanine, the active metabolite. Azathioprine acts during the S-phase of the cell cycle and inhibits the formation of adenine and guanine nucleotides. Azathioprine is metabolized by several enzymes, including hypoxanthine guanine phosphoribosyltransferase (HGPRT), xanthine oxidase (XO), and thiopurinemethyltransferase (TPMT). In those with low levels of TPMT, the drug will be more readily metabolized by the HGPRT pathway, leading to higher drug levels. Therefore, appropriate dosing depends on this enzyme level. Another consideration when prescribing azathioprine is to avoid certain drugs, such as allopurinol, which inhibits XO and shunts azathioprine metabolism toward the HGPRT pathway. This increases the risk of bone marrow suppression. Side effects from azathioprine are gastrointestinal toxicity, hepatotoxicity, alopecia, and pancreatitis. In addition, lymphoproliferative diseases and infection rates may be elevated. The use of combined prednisone and azathioprine is a commonly employed regimen in pemphigus and is usually well-tolerated. In Chams-Davatchi's RCT, disease control was achieved in 80% of patients in the cohort receiving azathioprine 2.5 mg/kg/day and prednisone 2 mg/kg/day after 1 year, and the cumulative steroid dose was significantly lower than that of the prednisone monotherapy and prednisone plus mycophenolatemofetil cohorts. (Femiano F, Gombos F, Scully C., 2002) However, another randomized trial comparing azathioprine 2 mg/kg/day with mycophenolatemofetil 2000 mg/day in 40 pemphigus patients failed to demonstrate any significant difference between the two therapies in terms of remission, relapse rates, cumulative steroid dose or adverse effects. (Beissert S, Werfel T, Frieling U et al., 2007) Azathioprine has been shown to have a steroid-sparing role and to reduce steroid-related complications. Its role in disease control has not been satisfactorily established, but based on the limited evidence azathioprine is beneficial.

##### MycophenolateMofetil

Mycophenolatemofetil (MMF) inhibits de-novo purine synthesis by noncompetitively inhibiting inosine monophosphate dehydrogenase (IMPDH). Both B-cell and T-cell lymphocytes are most affected by MMF because these cells lack a purine salvage pathway. Since the salvage pathway is still, this drug may be considered safer than

other immunosuppressive agents. Dosages range from 0.5 to 1.5g twice daily. After ingestion, MMF is converted to mycophenolic acid, which is metabolized by the liver. MMF is well tolerated, with side effect gastro-intestinal distress and dose-related and reversible anemia, leukopenia, and thrombo-cytopenia. Physicians must monitor CBC and liver enzymes monthly. Mycophenolatemofetil is a relatively recent drug that functions as an immunosuppressant by inhibiting the proliferation of lymphocytes. The largest case series, by Mimouni et al., reported 42 patients treated with mycophenolatemofetil 35–45 mg/kg/day in combination with prednisone, 1mg/kg/day. (Mimouni D, Anhalt GJ, Cummins DL et al. 2003) Remission was achieved in 27 out of 42 patients with a steroid dose of less than 0.15 mg/kg/day after a median of 9 months. The therapy was well-tolerated, with 77% of patients having no adverse effects. Overall, the evidence suggests that mycophenolatemofetil serves a steroid-sparing role and there is some evidence to suggest it may be superior to azathioprine in terms of disease control.

##### Cyclophosphamide

Cyclo-phosphamide is an alkylating agent that binds to DNA nonspecifically during the cell cycle. This nitrogen mustard derivative arrests the cell cycle and induces apoptosis in cells with a high mitotic rate, such as lymphocytes. It is metabolized by the hepatic cytochrome P450 system. The toxicity of cyclophosphamide is significantly higher than that of azathioprine and MMF, although many patients do not experience serious side effects. Acute myelosuppression, mucosal ulcers, alopecia, nephrotoxicity, cardiotoxicity, hepatotoxicity, and interstitial lung fibrosis. Rarely, male patients may develop azoospermia. Hemorrhagic cystitis occurs in up to 40 percent of patients and is associated with development of transitional cell carcinoma. This toxicity is due to the acrolein metabolite of cyclophosphamide. The risk of cystitis may be reduced with high fluid intake, frequent urination, mesna, and monitoring for hematuria. An RCT by Chrysomallis et al. compared prednisone 40 mg/day monotherapy and prednisone plus adjuvant cyclophosphamide 100 mg/day or ciclosporin 5 mg/kg/day. (Chrysomallis F, Ioannides D, Teknetzis A et al., 1994) In total, 48 patients with newly diagnosed mucosal PV were randomized to either prednisone 40 mg, prednisone with cyclophosphamide 100 mg/day or ciclosporin 5 mg/kg/day. There was no significant difference between the three cohorts in terms of time to remission or relapse rates.

##### Pulsed Cyclophosphamide

Pulsed intravenous cyclophosphamide has been reported to be more effective than oral cyclophosphamide in a number of autoimmune conditions. (Dhabhai R, Kalla G, Singhi MK, Ghiya BC, Kachhawa D., 2005; Haubitz M, Schellong S, Gobel U et al. 1999) offering improved clinical outcomes and fewer side effects than daily oral therapy. No studies to date have compared oral and pulsed cyclophosphamide. In Chams-Davatchi's RCT, 73.3% of patients in the pulse cyclophosphamide cohort achieved complete remission after 1 year and the cumulative steroid dose was significantly lower than that of the prednisone monotherapy cohort, indicating a potential steroid-sparing role of the modality. (Femiano F, Gombos F, Scully C., 2002)

##### Cyclosporin

Cyclosporine is an immunosuppressive agent with anti-T-cell lymphocyte activity. It forms a complex with cytoplasmic cyclophilin and blocks its ability to activate calcineurin. Activated calcineurin normally phosphorylates NFAT-1, a transcription factor that initiates IL-2 production and promotes proliferation of helper and cytotoxic T-cells. Laboratory monitoring consists of renal- and liver-function tests, electrolytes, lipid profile, and blood pressure. Cyclosporine has many potential side effects. The most common problems are electrolyte abnormalities, such as hyperkalemia, hyperuricemia, and hypomagnesemia. The drug is metabolized by the hepatic cytochrome P450 system and has the potential for many drug interactions. Cyclosporine is nephrotoxic, which is dose related and may initially be reversible. However, long-term use often leads to irreversible kidney damage and hypertension. Renal toxicity may be potentiated by concomitant use of aminoglycosides, nonsteroidal

anti-inflammatory drugs, amphotericin B, and vancomycin. Other side effects include tremors, hirsutism, hyperlipidemia, hypertension and gingival hyperplasia.

Two RCTs and a number of case series have presented the use of ciclosporin in pemphigus. Ioannides *et al.* reported an RCT of 33 patients with newly diagnosed pemphigus. (Ioannides D, Chrysomallis F, Bystryn J, 2000) Patients were randomized to treatment with prednisone 1 mg/kg (n = 17) or prednisone and ciclosporin 5 mg/kg (n = 16) and followed for 4–6 years. The RCT by Chrysomallis *et al.*, described previously in the discussion of cyclophosphamide, failed to demonstrate any benefit of adjuvant ciclosporin in the time to achieve disease control, the proportion of patients responding or treatment or relapse rates. (Pasricha JS, Sood VD, Minocha Y, 1975)

#### Methotrexate

Methotrexate is an antimetabolite that suppresses DNA and RNA synthesis during the S-phase of cell cycle. The drug competitively inhibits dihydrofolate reductase, which decreases the formation of tetrahydrofolate, a cofactor important in de-novo purine and thymidylate synthesis. Patients should be started on a low dose (often with an initial test dose) and cautiously increased every week to the target dose. The most common adverse effect of methotrexate is hepatotoxicity. Patients who have a cumulative dose >1.5g should undergo liver biopsy. Additionally, the drug may cause bone marrow suppression, ulcers, alopecia, interstitial pneumonitis and fibrosis, and nephrotoxicity. Predisposing factors for toxicity include alcohol consumption, renal insufficiency, diabetes, and increasing cumulative doses. An acute methotrexate overdose may cause bone marrow suppression or gastrointestinal mucositis. In these cases, folic acid can be administered as a rescue treatment. No controlled trials have yet been conducted investigating the efficacy of methotrexate in pemphigus. A retrospective analysis of the English literature to date found that 111 out of 136 (82%) pemphigus patients across seven studies demonstrated clinical improvement on methotrexate. (Gurcan HM, Ahmed AR, 2009)

#### Chlorambucil

One small retrospective case series has been reported investigating chlorambucil therapy. In the study, nine pemphigus patients (seven PV and two PF) were treated with chlorambucil and prednisone and six out of nine patients demonstrated clinical improvement. (Shah N, Green A, Elgart G, Kerdel F, 2000) The study suggests that chlorambucil may be a potential adjuvant in pemphigus when other immunosuppressants fail, but no recommendation can be made of its utility on this small series alone.

#### Gold

Gold is one of the oldest therapeutic agents, exerting anti-inflammatory properties and influencing humoral and cellular immunity. As it has a delayed onset of action, it is normally administered as an adjuvant therapy. Auad *et al.* reported a blinded, controlled trial of adjuvant gold in 30 PF patients. (Auad A, Auad T, 1986) Patients were treated with intramuscular gold thiomalate 50 mg weekly until disease control was established, and monthly injections thereafter for 4 months. Four patients were treated with gold monotherapy and 22 were treated with combined prednisone and gold. Response to therapy was reported in 22 out of 26 (85%) patients with a reduction of blisters and ability to taper steroids to less than 20 mg/day. Remission was reported in 11 out of 26 patients who were able to discontinue steroids and four of these patients were able to discontinue all treatment. Four out of 26 patients did not respond. Gold may be considered as a possible treatment option when other adjuvants cannot be employed.

#### Dapsone

Dapsone is a sulfone antibiotic with anti-inflammatory activity primarily against polymorphonuclear leukocytes. The drug inhibits neutrophil toxicity and chemotaxis by blocking myeloperoxidase activity.

Dapsone commonly causes a hemolytic anemia and methemoglobinemia in varying degrees in all patients. It is dose-

related. Dapsone is also associated with an idiosyncratic peripheral motor neuropathy and psychosis. Agranulocytosis is a rare, but serious reaction occurring in the first three months of therapy. Dapsone has been evaluated in one RCT of 19 recalcitrant PV patients reported by Werth *et al.* (Calebotta A, Saenz AM, Gonzalez F *et al.* 1999). Patients were randomized to receive maintenance steroids plus either dapsone 125–150 mg/day or placebo. In the dapsone cohort, five out of nine patients were able to taper their steroid dose below 7.5 mg/day compared with three out of ten in the placebo cohort, although this was not statistically significant.

#### Tetracyclines/Nicotinamide

Tetracycline and niacinamide may be combined to treat autoimmune blistering disorders, such as bullous pemphigoid. Tetracycline is an antibiotic that works through inhibition of the 30S ribosomal subunit. In addition to antibiotic activity, it possesses anti-inflammatory properties. Niacinamide is the amide of niacin (vitamin B3) and also is anti-inflammatory. The mechanism of action of their combined, immune-modulating properties is unclear. However, it is known that they inhibit neutrophil and eosinophil chemotaxis, which may downgrade the humoral response. Side effects from the drugs include gastrointestinal distress, pseudotumor cerebri, and photosensitivity from tetracycline. In addition, permanent discoloration may develop during tooth development, so tetracycline should not be given to children under nine years of age. Niacinamide has been associated with pruritus and flushing, especially if consumed with alcohol. Patients also may report nausea and headache and there may be drug-drug interactions, especially with lipid-lowering agents. The evidence for the use of tetracyclines and nicotinamide in pemphigus is derived from small case series. Calebotta *et al.* reported a prospective series of 13 hospitalized patients with PV treated with tapering regimens of tetracycline 2 g/day and prednisone 0.5–1 mg/kg/day and compared the study group with a historical cohort of seven pemphigus patients treated with prednisone and azathioprine. (Alpsoy E, Yilmaz E, Basaran E *et al.*, 1995) All patients in the study cohort achieved cessation of blister formation within 5.5 days compared with 23.7 days in the control cohort. The study cohort also had fewer new lesions after 2 weeks, could taper their steroid doses faster and had shorter hospital admissions (all results were statistically significant). Alpsoy *et al.* reported 15 patients with pemphigus (11 PV and four PF) treated with tetracycline 2 g/day and nicotinamide 1.5g/day over 2 months. (Chaffins ML, Collison D, Fivenson DP, 1993) That evidence regarding the use of antibiotics and nicotinamide in pemphigus.

#### Biological agents

##### Intravenous Ig (IVIg).

High-dose IVIG is a purified, human source of immunoglobulin G (IgG) from pooled plasma. Preparation of IVIG undergoes three independent processes for the inactivation and removal of viral contaminants, such as hepatitis and human immunodeficiency virus. It is administered as a slow, IV infusion at 2g/kg per cycle divided over 3 to 5 consecutive days. Treatment is repeated every four weeks. The mechanism is unknown although several theories exist. These include inhibition of Fc receptors, inhibition of autoantibody formation and neutralization of autoantibodies, complement and cytokine inhibition, and inhibition of the Fas-FasL interaction and apoptosis, and enhanced steroid sensitivity. There are several potential complications from IVIG. Patients with renal insufficiency are at risk for renal failure, so infusions must be given slowly and cautiously. In addition, transfusion-related acute lung injury (TRALI) is rare and if there is a previous history of infusion reactions, premedication with steroids or antihistamines is indicated. Other adverse effects are rare and include fever, headache, myalgia, nausea, tachycardia, hemolysis, aseptic meningitis, thrombotic event, and anaphylaxis in patients with IgA deficiency due to trace amounts of IgA in the preparation. Serum levels of IgA and hepatitis panel are screened before initiation of therapy. CBC and complete metabolic panel, including liver function tests, are monitored prior to each cycle. IVIG is very expensive and generally reserved for patients who do not respond or have serious adverse events from standard therapies. Intravenous Ig (IVIg) is being increasingly

employed in the treatment of recalcitrant pemphigus. There has been one RCT and several cases (Baum S, Scope A, Barzilai A, Azizi E, Trau H.:2006; Bystryń JC, Jiao D, Natow S.:2002; Harman KE, Black MM.:1999; Beckers RY, Brand A, Vermeer BJ, Boom BW.:1995; Segura S, Iranzo P, Martinez-de Pablo I, Mascaro J et al.:2007; Ahmed AR, Sami N.:2002; Amagai M, Ikeda S, Shimizu et al.:2009) describing its use. Amagai et al. have recently published a double-blinded, multicenter RCT of 61 pemphigus patients randomized to infusions of IVIg 400 mg/kg/day or 200 mg/kg/day, or placebo over 5 consecutive days.<sup>[42]</sup> A dose-response relationship was observed amongst the three cohorts with the time to leaving the protocol significantly prolonged in the 400-mg cohort compared with placebo. Both the 200-mg and 400-mg cohorts were reported to have significant decreases in pemphigus activity scores and autoantibody titers from baseline.

### Plasmapheresis

Plasmapheresis is hypothesised to remove pathogenic autoantibodies and has been used in refractory cases of pemphigus. The utility of plasmapheresis is controversial, with the results of one RCT ostensibly opposing those of small case series. Guillaume et al. randomized 40 previously untreated pemphigus patients to prednisolone monotherapy (0.5-2 mg/kg/day) or prednisolone plus ten large-volume plasma exchanges (55 ml/kg/exchange) over 4 weeks.(Roujeau JC, Andre C, Joneau Fabre Met al.:1983) No differences were observed between cohorts with respect to clinical improvement, cumulative steroid dose or autoantibody titers. Four patients in the plasmapheresis cohort died of sepsis or thromboembolism. These results differ to the outcomes reported in the case series and reports on plasmapheresis. Roujeau et al. described a retrospective case series of ten patients (two PF and eight PV) treated with massive volume plasmapheresis (3000-5000 ml/exchange).(Sondergaard K, Carstens J, Jorgensen Jet al.:1995) Which may explain the poor efficacy of plasmapheresis in the trial. Plasmapheresis may be considered for rapid control of severe or recalcitrant pemphigus as should the use of concomitant immunosuppression.

### Immunoadsorption

Immunoadsorption is a relatively new treatment, which, unlike plasmapheresis, specifically removes particular plasma components such as pathogenic immunoglobulins, enabling the treatment of larger volumes of plasma without the substitution of plasma components.(Luftl M, Stauber A, Mainka A, Klingel R, Schuler G, Hertl M.:2003) The evidence for this therapy is derived solely from case series. Luftl et al. reported a series of nine pemphigus patients (seven PV and two PF) treated with immunoadsorption in addition to their regular immunosuppressive therapy.(Eming R, Rech J, Barth S et al.:2006) All patients demonstrating rapid clinical improvement.

### Rituximab

Rituximab is a genetically engineered, chimeric, murine/human monoclonal antibody directed against CD20 antigen on the cell surface of normal and malignant B-cell lymphocytes. It is administered as an IV infusion, and premedication with acetaminophen and diphenhydramine should be considered to avoid infusion reactions. Several theories exist on the drug's mechanism of action. Among them is the drug's ability to inhibit autoantibody-producing B-cells in the immune system. Rituximab has several black box warnings due to serious adverse events that had fatal outcomes. These fatalities resulted from infusion reactions usually occurring within the first 24 hours of the first infusion, acute renal failure from tumor lysis syndrome, severe mucocutaneous reactions, and progressive multifocal leukoencephalopathy due to JC virus infection. Rituximab is an anti-CD20 humanized monoclonal antibody causing transitory B-cell depletion reserved for patients with pemphigus that is unresponsive to conventional therapies or for patients in whom these drugs are contraindicated. Several case reports and a number of small series describe patients treated with pemphigus on a regimen of four weekly infusions of rituximab 375 mg/m<sup>2</sup>. A retrospective review of the use of rituximab in PV identified 17 patients across ten reports, 88% of whom

demonstrated some improvement whilst on the therapy.(El Tal AK, Posner MR, Spigelman Z, Razaque Ahmed A:2006)

### Topical EGF

The efficacy of topical EGF has been evaluated in a double-blinded RCT of 20 PV patients.(Kaufman DB, Shapiro R, Lucey MR, Cherikh WS, T Bustami R, Dyke DB:2004) Patients had similar, symmetrical lesions treated with either EGF 10 µg/g in silver sulfadiazine cream or silver sulfadiazine cream alone. Lesions treated with topical EGF healed in a median of 9 days compared with control lesions which healed in a median of 15 days, with the difference found to be significant. Further studies are required to confirm these promising results before making an assessment of topical EGF in pemphigus.

### DISCUSSION

PV is an autoimmunity disorder with autoimmune, intraepithelial, blistering. The treatment of PV in any given patient may have several different goals, such as relief of symptoms, induction of remission in patients with active disease, prevention of relapse, healing of fistulas, and avoidance of emergency surgery. The current drug treatments include the use of anti-inflammatory agents, glucocorticoid agents and biological agent that reduce the symptoms associated with PV.

Therapy may be modified to some extent based on the severity and location of the disease. Generally treatment with glucocorticoid is common but having severe side effect on most of the patients like osteoporosis, osteonecrosis, cushingoid fat redistribution, and acid reflux disease. Now modified and new treatment with immunosuppressive and anti-inflammatory agent such as azathioprine, mycophenolatemofetil, cyclophosphamide and ciclosporin, Having less side effect and better option for PV treatment. Now, biological agent such as, IVIG, plasmapheresis, rituximab are alternative and now widely used.

### Abbreviations

GS- glucocorticosteroid hormone, PV- pemphigus vulgaris, IgG- immunoglobulin G, RCT- randomized controlled trial.

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