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Journal of Skin and Sexually Transmitted Diseases

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Review Article

Refractory pemphigus vulgaris: Treatment options

Reshmi Gangan

Department of Dermatology, Primary Health Care Corporation, Doha, Qatar.

***Corresponding author:**
Dr. Reshmi Gangan,
Department of Dermatology,
Primary Health Care
Corporation, Doha, Qatar.

reshgang@yahoo.co.in

Received : 01 May 19
Accepted : 24 June 19
Published : 02 December 19

DOI
10.25259/JSSTD_25_2019

Quick Response Code:

ABSTRACT

Pemphigus vulgaris is an autoimmune mucocutaneous blistering disorder characterized by the presence of pathogenic autoantibodies against adhesion proteins on epidermal keratinocytes called desmogleins (DSG1 and DSG 3). It has a chronic relapsing and remitting course and in severe cases can be life threatening. Those patients who fail to respond to traditional treatments are considered to have refractory pemphigus. This review focuses on various therapies that are currently in practice as well as in pre-clinical or clinical trials for steroid-resistant pemphigus vulgaris.

Keywords: Pemphigus, Corticosteroids, Azathioprine, Mycophenolate mofetil, Rituximab

INTRODUCTION

Pemphigus vulgaris is a potentially fatal autoimmune disease in which severe blistering of the skin and mucous membranes appears that can lead to malnutrition and sepsis.[1] Systemic immunosuppression with a combination of systemic glucocorticoids and immunosuppressive adjuvants constitute the first line treatment for these patients. Adjuvant immunosuppressive medications such as azathioprine, mycophenolate mofetil, dapsone, cyclophosphamide (both single and pulse dose), and cyclosporine are especially useful in extensive disease.[2] The response to treatment is evaluated on the basis of (1) cessation of new blister formation, (2) absent Nikolsky sign, and (3) healing of old lesions with re-epithelialization (all of which indicate control of disease activity).[3]

Consensus statement

International Pemphigus Committee has come out with the consensus statement of mutually acceptable common definitions for pemphigus.[4] Based on this consensus:

- Baseline is defined as the 1st day of therapy by the physician.
- Time from baseline to the time at which new lesions cease to form and established lesions begin to heal is considered as control of disease activity and it marks the initiation of the consolidation phase.
- End of consolidation phase is defined as the time at which no new lesions have developed for a minimum of 2 weeks, and approximately 80% of established lesions have healed. This is the point at which the clinicians start to taper corticosteroids.
- Absence of new or established lesions for at least 2 months while the patient is receiving minimal therapy is defined as complete remission on therapy.

- Minimal therapy is defined as ≤10 mg per day prednisolone or equivalent and or minimal adjuvant therapy for at least 2 months.
- Complete remission off therapy is defined as the absence of new and or established lesions for at least 2 months while the patient is off all systemic therapy.
- Relapse/flare is the appearance of 3 or more new lesions/month that does not heal spontaneously within 1 week or by the extension of established lesions in a patient who has achieved control of disease activity.

Step-by-step therapy after control of the disease

The European Dermatology Forum (EDF) proposed a usable treatment algorithm for use after the consolidation phase. One to three months are the time required for complete healing of the lesions.[5]

- Tapering of steroids is initiated once disease control is attained.
- Prednisolone is tapered by 25% once in 2 weeks. When the daily dose of prednisolone reaches 20 mg, further tapering is attempted more slowly. Most of the patients could be managed with 5 mg reduction every 4 weeks once it reaches 20 mg.
- The disease can be brought under control by raising the dose to the last effective dose, if <3 lesions reappear during tapering of oral corticosteroid therapy.
- If a patient relapses with the reappearance of more than three lesions, it is advised to increase oral corticosteroid therapy by going two steps back in the previous dose until disease control is achieved. Subsequently, tapering of systemic steroids is restarted. When unable to attain disease control, it is recommended to restart with the initial dose.
- Addition of an immunosuppressant is advised if oral corticosteroids are given as monotherapy.
- Patients who were already receiving combination treatment of systemic corticosteroids and an immunosuppressant may be treated by substituting the first line immunosuppressant with another one of the same group (azathioprine and mycophenolate mofetil) or by adding a second line immunosuppressant including immunoadsorption, intravenous immunoglobulin, or rituximab.
- Close monitoring is essential since prolonged immunosuppressive therapy increases the risk of side effects.
- It is prudent to remember that persistence of high levels of anti DSG1 IgG has a positive predictive value for skin relapse, whereas the persistence of anti-DSG 3 IgG does not necessarily predict a mucosal relapse.

Main adjuvants used in pemphigus vulgaris

1. Azathioprine – According to EDF guidelines, azathioprine is the first line adjuvant immunosuppressant in pemphigus. The recommended dose is 1–3 mg/kg/day and the required dose is based on the activity of the enzyme, thiopurine methyltransferase (TPMT) in the individual. This enzyme is involved in the metabolism of the drug. Patients with high levels of TPMT may be prescribed up to 2.5 mg/kg azathioprine, while adults with pemphigus vulgaris and intermediate or low TPMT levels, should receive a dose only up to 0.5–1.5 mg/kg/day. A dose of 50 mg/day could initially be administered, and if no idiosyncratic reactions occur, it could be increased after a week. Azathioprine should not be used in patients who lack TPMT activity. Azathioprine is primarily useful in pemphigus as a steroid-sparing agent. Coadministered azathioprine helps to attain remission with lower cumulative corticosteroid dose.[6]
2. Mycophenolate mofetil (MMF) – A safe steroid-sparing agent and a first line adjuvant immunosuppressant, the optimal dose of mycophenolate mofetil is weight dependent with a dose of 2 g/day for the average patient of 75 kg. Gastrointestinal adverse events may be avoided by progressively increasing the dose by 500 mg/week, to reach the final dose of 2 g/day. MMF in combination with prednisolone seems to be more effective in patients with relapse of pemphigus vulgaris or in cases of refractory pemphigus.[7]
3. Cyclophosphamide – Useful as second-line immunosuppressant adjuvant therapy as per the EDF guidelines, this alkylating agent acts by preventing cell division by crosslinking DNA strands and by decreasing DNA synthesis. It is a cell cycle phase non-specific agent having a potent immunosuppressive activity that causes a reduction in autoantibody production. High rates of successful treatment of pemphigus with a pulsed regimen of dexamethasone and cyclophosphamide {monthly infusion of dexamethasone (100 mg for 3 days) and cyclophosphamide (500 mg for 1 day) plus daily 50 mg dose of oral cyclophosphamide in between pulses} has been documented.[8]

In dexamethasone cyclophosphamide pulse treatment (DCP), once clinical remission is achieved pulse treatment is given for 9 more months followed by 50 mg cyclophosphamide per orally daily for the next 9 months.[8] Another regimen of pulse cyclophosphamide is 1000 mg IV dose once per month for 6 months and every other month thereafter along with prednisolone (2 mg/kg/day followed by a taper).[9] Oral dosing of cyclophosphamide is 2–3 mg/kg/day.

Adverse effects of treatment include myelosuppression, systemic infections, bladder toxicity, increased risk of malignancies, and premature gonadal failure.

4. Dapsone – recommended in a dose of 100 mg/day or up to ≤1.5 mg/kg/day as a steroid-sparing agent, it is used to achieve a reduction in dosage of steroids to

7.5 mg/day or less of prednisolone equivalent. However, no benefit is reported on achieving remission of the disease. It is recommended to test serum G6PD (glucose six phosphate dehydrogenase) activity before initiating therapy with dapsone.[4,10]

5. Methotrexate – At a dose of 10–20 mg/week, it is used as a steroid-sparing agent.[4]

Pemphigus that fails to respond sufficiently to optimal administration of these immunosuppressives is referred to as refractory pemphigus.[3] These patients include: (1) Patients who fail to respond to the first-line and second-line regimens, (2) patients with contraindication to the first line and second-line regimens, and (3) patients who are unable to tolerate first-line drugs and are not suitable candidates for the second-line treatment.

Interventions that directly target the antibody-mediated pathogenesis of pemphigus such as rituximab, intravenous immunoglobulins (Ig), immunoadsorption, plasmapheresis, and intralesional immunomodulators are made use of, in the management of refractory pemphigus.[3,11,12]

Treatment options

The treatment selection in refractory pemphigus is depended on the availability of a particular therapeutic option, which, in turn, is based on the accessibility to treatment and the facility to administer it safely. Use of intravenous IgG, plasmapheresis, immunoadsorption, and rituximab are limited by their cost while side effects and toxicity might be the limiting factor in case of cyclophosphamide.[12]

Management of refractory pemphigus is best made by immune-suppressive regimen, which itself based on systemic glucocorticoids with or without a first-line adjuvant medication.[10,12] Adjuvant therapy as such reduces the risk of relapse in pemphigus.[13]

Rituximab is a monoclonal antibody directed against CD20 antigen on B lymphocytes. This attains long-lasting B cell depletion. A dose regimen similar to that used in the treatment of rheumatologic disease (1g infusion on day 1 and day 15 of treatment) is administered in combination with a tapering dose of systemic glucocorticoids.[14-16] 500 mg at month 12 and every 6 months thereafter or based on clinical evaluation is the recommended maintenance therapy. The recommended schedule for relapses is at a dose of 1000 mg. The systemic glucocorticoid may be resumed (if already discontinued) or increased after clinical evaluation.[5] Intravenous methylprednisolone (100 mg) or an equivalent glucocorticoid should be given 30 min before each rituximab infusion.[15] Rituximab is also found beneficial for the initial treatment of pemphigus when given in combination with prednisolone.[17]

The median time to complete remission (defined as an absence of new or established lesions) is recorded as 70 days (range 30–150 days). The documented median time to relapse is 16 months (range 6–41 months).[17] Additional doses of rituximab are found effective in relapsed cases or in patients who fail to achieve remission after a single cycle of rituximab.[17]

Lymphoma dosing of single cycle rituximab (375 mg/m^2 once weekly for 4 weeks) has a beneficial effect on refractory pemphigus.[18]

Other protocols of rituximab

Low dose

Rituximab (500 mg doses of rituximab taken twice separated by 2 weeks) is found effective and safe for pemphigus but has a greater risk for relapses, mostly at the end of 2nd year. It also has a significantly higher cumulative requirement of coadministered immunosuppressant like azathioprine.[19]

Intralesional rituximab

Limited data suggest that intralesional rituximab may be an effective treatment modality for refractory oral pemphigus at dose 5 mg/cm^2 on days 1 and 15.[19]

Combination therapy of rituximab

Rituximab when combined with IVIG or immunoadsorption is reported to have a fast onset of action with rapid clinical remission and long-term control in difficult to treat pemphigus.[16,20] Rituximab is suggested as therapeutic option in patients who remain dependent on more than 10 mg prednisolone combined with an immunosuppressive adjuvant.[5]

Adverse effects of rituximab

Adverse effects of Rituximab are infection, progressive multifocal leukoencephalopathy, infusion reaction, deep vein thrombosis, pulmonary thromboembolism, long-term hypogammaglobulinemia, and neutropenia.[14]

Intravenous immunoglobulin – Is effective for refractory pemphigus, it is used as adjuvant therapy to systemic corticosteroids and immunosuppressive adjuvants. However, the mechanism through which IVIG improves pemphigus is not clearly understood. Proposed mechanism includes a reduction in circulating pemphigus autoantibodies by stimulating an increase in the catabolism of immunoglobulins.[21] The usual dose of IVIG is 2 g/kg/cycle administered over 2–5 consecutive days, monthly. Treatment is given over several days so as to avoid adverse effects such as headache and nausea.[22]

For glucocorticoid resistant pemphigus (defined as a failure to respond to the equivalent of 20 mg/day or more of prednisolone), 400 mg/kg of IVIG for 5 consecutive days, is found useful.[22]

Side effects to IVIG include headache, back pain, increased blood pressure, and abdominal discomfort.[22] Aseptic meningitis is a serious side effect of IVIG therapy that requires immediate termination of treatment. Anaphylaxis is a potential risk of IVIG treatment in patients with IgA deficiency.[22]

Immunoadsorption- It is a therapeutic option for pemphigus. It exerts effect through the removal of circulating autoantibodies (IgG) with very high specificity. High cost and non-availability in some countries have limited the use of this modality.[23]

Many apheresis systems for immunoadsorption have been successfully applied in pemphigus. Regenerative adsorber such as Protein A or synthetic ligands such as PGAM 146 and Globaffin that have a high affinity to the Fc portion of human IgG is found to be most effective.[23]

The adsorber protocol determines the advantages of immunoadsorption for eliminating pemphigus autoantibodies.[20] Immune adsorption is repeated every 3–4 weeks in short immunosuppressive therapies of 3–4 day cycles. The initial response to treatment can be rapid, occurring within a few weeks and benefit most patients with extensive skin involvement. Adverse effects are hypotension, bradycardia, anaphylaxis, and sepsis from a central catheter.[23]

Plasmapheresis – It is a commonly used therapy. Unlike immunoadsorption, which specifically removes circulating IgG, plasmapheresis (plasma exchange) non selectively removes plasma proteins from circulation.[24] Plasmapheresis is done by extracorporeal blood purification techniques – blood is continuously removed from the patient and separated into cellular components and plasma; the cellular parts are returned to the patients along with replacement fluid like albumin. Plasmapheresis is an effective adjuvant therapy in severe pemphigus vulgaris patients for disease activity control by reducing serum levels of autoantibodies.[21] It can be performed using special devices for centrifugation. There is no standardized protocol for the number and frequency of sessions; usually, 4–5 plasma exchanges, each consisting of 1–1.5 volumes, over 7–10 days constitute an adequate short-term therapy for removing 90% of the total body immunoglobulin content.[25]

Extracorporeal photochemotherapy – Is done using mononuclear cells isolated with a cell separator. They are irradiated with ultraviolet A(UV-A) light in the presence of 8 methoxy psoralen, and the treated cells are returned to the patient.[26]

Infliximab – It is a chimeric monoclonal antibody against TNF alpha (Tumor Necrosis Factor alpha). TNF-alpha is strongly expressed by the acantholytic cells in pemphigus vulgaris. When infliximab and prednisolone are used together in the treatment of pemphigus, though better results were obtained, the trends were not statistically valid.[23] Same results have been obtained with Etanercept, another TNF-alpha inhibitor.[27]

Other therapies for pemphigus includes:

- Topical tacrolimus and pimecrolimus
- Sulfasalazine with pentoxifylline
- Gold
- Tetracyclines with or without nicotinamide
- Chlorambucil
- Mizoribine[28]
- Subcutaneous veltuzumab.[29]

Potential future treatments:[30]

- Chimeric Antigen Receptor Therapy
- T cell immunotherapy
- BAFF (B cell activating factor) and APRIL (A proliferation-inducing ligand) inhibitors
- P38 MAPK (Mitogen-activated protein kinase) signaling pathway inhibitors
- Bruton's tyrosine kinase inhibitor.

CONCLUSION

Meticulous research on the immunology and cell biology of pemphigus vulgaris should be a top priority since safer and more effective treatment options are the need of the hour for this potentially fatal autoimmune disease.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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How to cite this article: Gangan R. Refractory pemphigus vulgaris: Treatment options. J Skin Sex Transm Dis 2019;1(2):61-5.