Review Article

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THE PRELUDE ON CONVENTIONAL AND ADVANCE TREATMENT OF PEMPHIGUS VULGARIS (PV): A REVIEW

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ABSTRACT

The Pemphigus vulgaris (PV) is a group of highly lethal autoimmune disease characterized by mucocutaneous erosions or blisters. Pemphigus vulgaris can be present in different forms like oral and topical. So, it is challenging to manage and treat. Mortality rate due to Pemphigus vulgaris can be decreased by using systemic corticosteroids, but the present treatment options are limited due to the toxicity profiles of drugs available for treating Pemphigus vulgaris. Recent studies that shed light on the molecular mechanisms involved in the disease had lead to introduction of advance therapies like immunoabsorption, extracorporeal photochemotherapy (ECP), tumor Necrosis Factor- α (TNF- α) treatment and few other treatments have been subject to randomized control trials to firmly establishes therapeutic efficacy. The present review emphasized on management of the condition, most commonly conventional treatments and recent treatment advances.

Keywords: Conventional and Advance therapy, Extracorporeal photochemotherapy, Immunoabsorption, Pemphigus Vulgaris, Rituximab.

INTRODUCTION

Pemphigus Vulgaris (PV) is a rare, chronic life-threatening autoimmune blister disease of the skin and mucous membrane.¹ It is caused by IgG autoantibody that binds to a membrane antigen (Dsg1/Dsg3) and is responsible for the release of a protease that leads to destruction of epidermal keratinocyte desmosomal caderins Dsg3/Dsg, resulting in loss of adhesion between the cells of epidermis, a phenomena called acantholysis.² The exact cause of this was unknown. Acantholysis along with direct immunofluorescence (DIF) evaluation revealing the presence of IgG deposits in intraepidermal keratinocytes, with a honeycomb pattern. It is usually fatal if untreated.³ Females aged 40-60 years are mostly affected. Pemphigus vulgaris is a one of the more severe presentations that very often leads to serious patient conditions that are difficult to handle on an outpatient basis, and repeatedly requires intensive care.⁴ Pemphigus vulgaris has worldwide distribution affecting 0.1–0.5 patients per 100000 populations per year. In the United Kingdom, a regional study estimated an incidence of 1.4 per 100 000 person years.⁵ Wide variation in mortality is reported, with one year mortality varying between 6 % in the United States and 41 % in France. In the few hospital based studies of the epidemiology of PV, the reported incidence varied between 0.076 and 1.6 per 100000 person years. A Pub med search (with search terms pemphigus and India) retrieved 96 articles (retrieved August 6, 2010) with earliest one dating back into 1960 in which Desai and Rao had described 21 cases of pemphigus.⁶ The Pemphigus vulgaris is frequently disaster with a death rate ranging from 65 % to 90 %, while the use of systemic corticosteroids and other advanced therapeutic methods have been reduced

approximately 10 % of the mortality rate.^{7,8} The current mortality was about 6.2 % (range 0 to 10 %) and did not show further significance reduction.^{9,10} Initially the minimum dose used for systemic therapy to control the disease, modifying the treatment by taking account of the general health and age of the individual patient and extent of the disease. Some while have more aggressive disease and need significant immunosuppressant. The mainstay of treatment remains to be corticosteroids with or without another adjuvant therapy. The adjuvant therapies include steroids sparing agents (immunosuppressive agents and anti-inflammatory agents), immunomodulatory procedures, Extracorporeal photo chemotherapy (ECP), Immunoabsorption, Tumor Necrosis Factor- α (TNF- α) antagonist and cholinergic agonist therapies.

Conventional Treatment

Treatment first aims to acquire disease remission, and this is regularly possible as a result of intensive therapy (often on an in-hospital basis). Such management is then followed by maintenance therapy to stabilize the disease with the administration of systemic medication in gradually decreasing doses.

Corticosteroids

The oral corticosteroids (CS) are used for the management of Pemphigus vulgaris. The initiation of corticosteroids was in 1950. For the administration of corticosteroids in Pemphigus vulgaris there is no standardized approach, the most common method is oral corticosteroids. The recent study the outcomes have continued to improve the mortality was zero and 29 % of patients' shows complete remission rate treated with steroids alone. On average, cessation of blistering takes 2-

3 weeks and full healing may take 6-8 weeks.¹¹ The initial dose of prednisolone is 120-180 mg per a day. The patients with severe Pemphigus vulgaris initial therapy with low- dose prednisolone 45-60 mg day were compared with high-dose prednisolone affecting more than 50 % of their body surface. In 5 years duration there was no significant difference in remission and relapse rate.¹² According to disease severity a tailored dosing schedule has been recommended.¹¹ The initial prednisolone doses of 40-60 mg day⁻¹ used for the patient with disease and in more severe cases, 60 -100 mg day⁻¹. If there is no response within 5-7 days, the dose should be increased in 50-100 % increments until there is disease control. If dose above 100 mg per a day is required, pulsed intravenous corticosteroids could be considered.¹⁰

Pulsed intravenous corticosteroids

The term “pulse” refers to discontinuous intravenous infusion of supra therapeutic drug doses in a short period of time. It achieve more rapid and effective disease control is main theoretical aim of pulsing.¹³ Pulse therapy is recommended as an adjuvant to the initial management plan for patients with more severe Pemphigus vulgaris involvement. Pulsed intravenous corticosteroids used for the intermittent administration of high dosed intravenous corticosteroids, usually methylprednisolone 250-1000 mg or equivalent dose of dexamethasone given on one to five consecutive days.¹⁴ Patients with oral Pemphigus vulgaris have given Prednisolone/Cyclophosphamide (100 mg) and Prednisolone/Cyclosporine (5 mg/kg), in those patients for the remission and relapse rates there was no significant change. However, cyclophosphamide and cyclosporine were given for a small period of only 2-3 months. The side-effects mainly associated with the use of pulsed intravenous corticosteroids are gonadal damage, teratogenicity, hemorrhagic cystitis, leucopenia and reversible alopecia and myelosuppression.¹⁵

Adjuvant Therapy

One of the treatment options for Pemphigus vulgaris includes adjuvant drug therapy, which are agents that support the effect of steroids administered mainly via the oral route. Some of these adjuvants act as “steroid sparing agents”. The foremost representatives are azathioprine and cyclophosphamide. Some of the characteristics of these drug substances will be dealt briefly.

Azathioprine (AZT)

Azathioprine (AZT) is used as an adjuvant drug in PV and also allowed to bring reduction in the dose of the steroid use and its side-effects.^{16,17} The complete remission rates of 28-45 % and mortality rates of 1.4-7 %, exceeds in patients treated with CS alone.¹⁰ In some cases AZT was effectively used as a monotherapy to induce and maintain clinical remission with a fall in antibody titre.¹⁸ AZT doses of 1-3 mg/kg⁻¹ used in previous studies based on the individual activity of TPMT (Thiopurine MethylTransferase) should be titrated ideally. Patients with very low TPMT levels (1:200-300 of the general population) AZT are best avoided¹⁹ and dose should be reduced doses to 0.5 mg/kg⁻¹. According to clinical and

side-effects, the dose should be titrated upwards up to 3.5-4 mg/kg⁻¹.²⁰ The side effects of AZT include bone marrow depression, liver dysfunction and increased incidence of malignancy. AZT is metabolized by TPMT and the low enzyme activity leads to accumulation of cytotoxic thiopurine metabolites which increase the risk of toxicity.²¹

Pulse cyclophosphamide

Pulse therapy was first described by Pasricha and Ramji (father of pulse therapy) in 1984.¹¹ It defined as discontinuous or intermittent Intravenous infusion of very high doses (mega doses) of drugs over a short time on arbitrary.²² The main aim of pulsing of cyclophosphamide is to achieve more effective and rapid control of disease compared with continuous drug, thus reduction in long-term maintenance corticosteroid doses and its side effects.²³ Though some authors feel that cyclophosphamide is more effective (an alkylating agent that disrupts cell growth and mitotic activity by cross linking DNA) compared to azathioprine, it is more difficult to use and has more lethal effects.^{10, 24} A number of factors have contributed to the success and widespread acceptance of dexamethasone pulse therapy. One most important factor was the choice of corticosteroid. Conventionally, methylprednisolone was the agent most commonly used in corticosteroid pulse therapy. The choice of dexamethasone made the treatment considerably more affordable and accessible to patients.^{25,26} The high doses of intravenous CS and cyclophosphamide are administered intermittent, usually three daily doses of dexamethasone (100 mg) or methylprednisolone (500-1000 mg) and single dose of cyclophosphamide 0.5-1.0 g/m² body surface area (starting dose 500-1000 mg and maximum dose 750-2000 mg) given monthly.²⁷ 300 patients with pemphigus (250 with PV) treated with dexamethasone and cyclophosphamide pulse (DCP) therapy at 4 weekly intervals. Overall, 190 patients (63 %) achieved complete remission, 48 % for more than 5 years. The overall mortality rate was less than 5 %. The steroid side-effects were very less but 62 % of menstruating female (18 of 29) amenorrhoea and azoospermia was developed and 55 % of patient (17 of 33) had pituitary-adrenal suppression.²⁸ A study was conducted in All India Institute of Medical Sciences (AIIMS) Twenty-nine of the 30 patients in whom DCP was instituted showed a good response and completed phase I in an average of 8 pulses.²⁹

Cyclosporine

Cyclosporine was useful adjuvant with steroid-sparing effects in PV.³⁰ Cyclosporine is an immunosuppressive agent with anti-T-cell lymphocyte activity. It inhibits production of interleukin-2 (IL-2) and interferon-gamma (IFN-g) by lymphocytes.²¹ Some recent single randomized, prospective, controlled trial studies on cyclosporine produced conflicting (an incompatible) results in 33 patients comparing methylprednisolone with cyclosporine 5 mg/kg⁻¹ Vs. oral methylprednisolone. 1 mg/kg alone found no statistically significant difference in outcome measures and there was no significant difference in terms of response, time required to control

the disease and proportion of flare between two groups of patients taking steroid versus steroid plus cyclosporine. More side effects were encountered with cyclosporine during a mean follow-up period of 5 years.³¹ There were no deaths but some patients were in complete remission but showed some side-effects like renal function impairment (dose dependent increase in urea and creatinine in the first week), hypertrichosis, gingival hypertrophy and tremor. On the basis of current evidence, cyclosporine cannot be preferred as an adjuvant drug in PV.^{32,33}

Methotrexate (MTX)

It is most widely accepted as an adjuvant. The methotrexate used as a monotherapy for PV. Methotrexate (MTX) is an antimetabolite that suppresses DNA and RNA synthesis during the S-phase of cell cycle. The drug competitively inhibits dihydrofolate reductase (DHFR), which decreases the formation of tetrahydrofolate (THF), 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 high doses of MTX (up to 125 mg a week are advised) combination with prednisolone 0.5-1.0 mg/kg/day to bring the disease under control within 6 months.³⁴ In practice it is difficult to use because of its side effects (mainly at hepatic level) thus, MTX as adjuvant is reserved for those cases of PV in which it is not possible to use with some other adjuvant substance such as azathioprine or cyclophosphamide.³⁵ The adverse effects reported were nausea and mild elevation of transaminase enzyme levels, myelosuppression, and stomatitis.

Mycophenolate mofetil (MMF)

Generally Mycophenolic acid used for the management of psoriasis during the last three decades, at present it has been re-formulated as mycophenolate mofetil (MMF) and used as an immunosuppressor in transplantation patients (Food and Drug Administration (FDA) 1995).³⁶ In recent years study found MMF to be useful in the management of ampullar lichen planus, systemic lupus erythematosus (SLE) and PV.³⁷ The current uses of mycophenolate in PV (It inhibit the de novo pathway of purine synthesis in T-lymphocytes and B-lymphocytes) administered as co-adjuvant daily doses of 2-2.5 g are typically given in to two divided doses with prednisolone to reduce the activity of PV. MMF shows only minimal side effects like diarrhoea, dyspepsia, nausea, myelosuppressive and those due to immunosuppression.^{38,39} Although it was initially used in monotherapy with positive effects over more than 6 months, it is now better used as adjuvant in case of active PV. MMF is recommended for recalcitrant cases, or when azathioprine and cyclophosphamide cannot be used.^{40,41}

Anti-Inflammatory Drugs

Dapsone (DDS)

Dapsone (DDS) is the one of most useful sulphonic antibiotic drug in application to many diseases, including leprosy. Mainly DDS was recommended to be an effective adjuvant to corticosteroids in PV.⁴² DDS exhibits

antibiotic effect, interferes with neutrophil chemotactic migration (blocking myeloperoxidase activity), reduce the release of prostaglandins (PGs) and leukotrienes (LTs), inhibit neutrophil adherence to basement membranes, inhibit the generation of toxic radicals and protect cells from neutrophil (inhibits neutrophil toxicity) and eosinophil-mediated injuries. The some of an experimental studies suggested that DDS exhibits no effects upon serum antibody levels in PV.⁴³ It showed no significant use in monotherapy, but can be used as adjuvant. A common side effect of DDS includes hemolysis, methaemoglobinemia, neuropathy and allergic dermatitis.⁴⁴

Gold

Gold was first described in the treatment of PV since 1973. In most of studies gold was used intramuscularly (i.m) in PV, a dose of 50 mg/week was used initially. If test dose is tolerated, it was used successfully as monotherapy. Gold (50 mg) was given weekly after test dose, and dose was reduced monthly when prednisolone was taken off. The complete remission rates were 15-44 % but side-effects lead to drug withdrawal in 17-35 % patients and it was found ineffective in 28 % of case. Its use seemed to be decreased recently due to concerns of its safety and efficacy. Major side-effects of gold are dermatitis, diarrhea, oral ulcer, proteinuria, blood disorders, alopecia, peripheral neuritis, pulmonary fibrosis and cholestatic jaundice.⁴⁵

Plasmapheresis

As the disease activity of PV generally correlates with the level of circulating autoantibodies, their removal seems a reasonable therapeutic approach. Plasmapheresis is mainly hypothesized to eliminate pathogenic autoantibodies and used in refractory cases of pemphigus. The disease activity of PV is generally estimated by the level of circulating autoantibodies and their removal seems a reasonable approach to treat PV and this can be done using plasmapheresis. The level of circulating antibodies was shown to increase as early as three hours after plasmapheresis. Therefore immunosuppressives are administered immediately after plasmapheresis to help achieve complete reduction. Patients who were treated with plasmapheresis and they followed by pulse cyclophosphamide or pulse methyl prednisolone with azathioprine showed some remission.⁴⁶ The circulating intercellular antibody titres decreased on average by three fold, 60 days after plasmapheresis. There was no data comparing the choice of immunosuppressive agents and the results suggested that the timing and the individual's responsiveness to the agent was the key to reduce antibody level.⁴⁷

Intravenous Immunoglobulins (IVIGS)

Intravenous immunoglobulin (IVIG) is being increasingly used in immune-mediated diseases (mainly functional blockade of Fc receptors, elimination of immune complexes, anti-idiotypic suppression of autoantibodies, and inhibition of complement mediated damage).^{48,49} Doses of 1.2-2 kg⁻¹ divided over 3-5 days were infused every 2-4 weeks. It was helpful in inducing a rapid

remission and clinical improvement in some cases, but may be temporary unless repeated courses of IVIG are studied.^{50,51} IVIG was initially used as an adjuvant therapy. There are important considerations for the use of IVIG. The drug is costly and often requires hospitalization for intravenous administration. There is no randomized control trial and the optimal dosage and regimen is yet to be determined. Long-term follow up data is important in defining its benefits. IVIG is usually well tolerated but the side effects include vasomotor symptoms such as headache, myalgia, flushing, and nausea. Anaphylactic shock may occur in patient with IgA deficiency.⁵¹

Advance Treatment

Immunoadsorption (IA)

Immunoadsorption (IA) is a relatively new treatment, which, unlike plasmapheresis specifically removes particular plasma components such as pathogenic immunoglobulins. Immunoadsorption consists of collecting patient plasma, passing it through an adsorber column (i.e., Protein A) to remove circulating immune complexes, IgG and returning the filtered plasma to the patient.⁵² The evidence for this therapy is derived solely from case series, Luftl *et al* reported a series of nine pemphigus patients treated with Immunoadsorption in addition to their regular immunosuppressive therapy.⁵³ Evaluation by ELISA revealed a 30 % reduction of pathogenic IgG antibodies after a single Immunoadsorption treatment, all patients were clinically improved. Some patients were allowed to remain on concomitant one cycle of immunosuppressive therapies like azathioprine or MMF, IA resulted in decline of desmoglein-specific IgG autoantibodies resynthesis and a dramatic clinical response.⁵⁴ More recently, a small case series demonstrated to achieve long-term remission. IA in combination with rituximab could be used.⁵⁵

Rituximab (RTX)

Rituximab (RTX) is a chimeric murine/human IgG1 anti-CD20 monoclonal antibody that targets pre-B and mature B lymphocytes, causing transitory B-cell depletion in patients suffering with PV, which is unresponsive to conventional therapies or for patients in whom other drugs are contraindicated. RTX prevents the maturation of antibody-producing plasma cells by reducing circulating B cells. Multiple case reports suggest that an effective treatment option for PV is RTX.⁵⁶ A study involving small series of patients treated on a regimen of four weekly infusions of RTX 375 mg/m² showed significant results. Most adverse effects were infusion related and temporary, although death occurred in one patient and systemic infection in another three were observed. The RTX used in combination with IVIG is highly effective in a series of eleven patients with extensive controlled PV. In some case studies the clinical remission lasted between 22-27 months with combination therapy.⁵⁷

Extra corporeal photo chemotherapy (ECP)

Extracorporeal Photochemotherapy (ECP) is also known as photopheresis, used in the treatment of patient following acute allograft rejection in cardiac, lung, renal, or liver transplantation, acute and chronic graft-versus-

host disease (GvHD), systemic lupus erythematosus (SLE), rheumatoid arthritis (RA) and PV.⁵⁸ Limited data has been published regarding the use of ECP in a variety of autoimmune diseases. The processes mainly involved in this leukapheresis means patient's white blood cells (WBC) were collected and exposed to 8-methoxypsoralen, after that cells are irradiated with ultraviolet-light (UV) and re-infused into the patient. Finally ECP inhibits the production of pathogenic autoantibodies of B-lymphocytes.⁵⁹ However, all three patients experienced relapses for which therapy with ECP was resumed.⁶⁰ In these studies patient treated with ECP showed a significant clinical improvement and showed no adverse effects.

Tumour necrosis factor- α (TNF- α) antagonists

Tumour necrosis factor- α (TNF- α) antagonists are helpful for the treatment of PV. Recent investigational studies have demonstrated that TNF- α plays an important role in the acantholysis process.⁶¹ Two case reports stated that infliximab was used successfully against refractory PV. The clinical improvement of disease increased by the use of etanercept was shown by two additional case studies. Clinical trials for both infliximab and etanercept are currently underway.^{62,63}

Cholinergic agonists

Research suggests that acetylcholine and its receptors are involved in the process of acantholysis in PV.⁶⁴ Up to now only 2 clinical studies have been performed. In a case study of 6 patients with active PV, the cholinergic agonist pyridostigmine bromide showed clinical improvement in 50 % of patients.⁶⁵ Two patients were able to control their disease with pyridostigmine bromide alone and 1 patient was able to remain in remission devoid of any medication. In a recent double-blind placebo controlled trial 3 PV patients with a total of 64 lesions were treated with 4 % pilocarpine gel reported a higher epithelialization index compared to placebo.⁶⁶

Topical epidermal growth factor (EGF)

The topical epidermal growth factor (EGF) has been evaluated in double-blinded RCT (Randomized Control Trials) of 20 PV patients. Patients had similar, symmetrical lesions treated with either EGF 10 μ g/g in silver sulfadiazine cream or silver sulfadiazine cream alone. Lesions treated with topical EGF healed in a median of 9 days compared to 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 PV.⁶⁷

Other Experimental Therapies

The other experimental therapies developed to suppress the production of anti-desmoglein 3 antibodies through inactivation and/or removal of disease-associated CD4+ T lymphocytes by using intravenous desmoglein 3 peptides.⁶⁸ A novel therapy, KC706 (Kemia, Inc.) is an oral allosteric p38 mitogen-activated protein kinase (p38MAPK) inhibitor. In a murine model of pemphigus p38MAPK inhibitor prevented blister formation.⁶⁹

Clinical trials are underway to determine the safety and efficacy of KC706 in the management of PV.

CONCLUSION

While many treatments have been developed for Pemphigus Vulgaris (PV), none of them have been shown to offer absolute success in controlling the disease. The treatment of choice is steroidal therapy via the oral or intravenous route, which offers an adequate response and can be favorably modified after prognosis. Pulse therapy appears to be novel path breaking therapy for treating PV along with other autoimmune and systemic diseases. In India, most of the hospitals prefer pulse therapy to treat patients suffering with PV. Conventional immunosuppressive and anti-inflammatory agents such as azathioprine, mycophenolate mofetil and cyclosporine are associated with severe adverse events. At present research directed towards better understanding of PV pathogenesis and introduction of a number of advance therapies such as Immunoadsorption, RTX. TNF- α antagonists is showing potential in PV treatment and management. Randomized controlled trials are the need of the hour to established safety and efficacy of these newer therapies in the management of PV.

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