Editorial

Treatment of pemphigus: An Indian perspective

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Pemphigus is a chronic autoimmune epidermal blistering disorder with potentially fatal outcomes. Unfortunately, in India pemphigus occurs at a younger age as compared to western countries and tends to be more severe. A significant proportion of pemphigus patients have been less than 40 years of age.[1] It is a common disorder in India; however there is lack of population based studies and most studies are hospital based. The incidence of pemphigus among the dermatology outpatient attendees has varied widely, 0.09-1.8%.[1,2] A clinic based study from Kerala estimated the incidence of pemphigus in Thrissur district as 4.4 per million population.[3]

Pemphigus has a considerable effect on quality of life of patients as well as their family members. With a chronic course of relapses, remissions, and a mortality rate between 5-10%, it poses a challenge for treatment. Mortality due to pemphigus which was as high as 90% decreased remarkably, with aggressive and widespread use of corticosteroids. High dose corticosteroids were once used in combination with other immunosuppressants with good improvement, but such high doses of corticosteroids were often associated with severe side effects, and was responsible for the death of nearly 10% of the patients.[4] With the aim of reducing the adverse effects of long term, high dose steroid administration, dexamethasone cyclophosphamide pulse (DCP) therapy was introduced in 1984.[5] Since then DCP or oral corticosteroids with or without adjuvant immunosuppressants have been the cornerstone of therapy for these disorders in India.[6,7] However, there has been a constant search for newer therapeutic modalities in pemphigus, to limit the corticosteroid requirement, to achieve early and long lasting remission and for better safety profile. Currently we are at the cross roads of a shift in managing our pemphigus patients with novel targeted therapeutic agents like rituximab (chimeric monoclonal antibody against CD 20 antigen) and intravenous immunoglobulin (IVIG) being increasingly used in India. At this critical juncture it is important to have an overview on therapeutics of pemphigus in an Indian context.

The choice of therapy from the available armamentarium depends on the severity of the disease, availability and affordability of the drug or facilities, associated comorbidities and the physician's preference. We follow a three tier approach in the management of our pemphigus patients.[8] Patients with mild disease, who may not require long term, high dose corticosteroids are managed by conventional modalities. Low dose corticosteroids (0.75-1 mg/kg/day) in combination with other steroid sparing adjuvants like azathioprine, cyclophosphamide and mycophenolate mofetil are prescribed. Depending on the treatment response, daily corticosteroids are gradually tapered and adjuvants are continued until remission is achieved. The choice of adjuvant depends mainly on efficacy, contraindications, drug interactions and affordability. Chams-Davatchi *et al.*,[9] conducted a four arm study comparing the efficacy of prednisolone alone, prednisolone plus azathioprine, prednisolone plus mycophenolate mofetil, and prednisolone plus intravenous cyclophosphamide pulse therapy. The authors found that the efficacy of prednisolone was

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enhanced when used in combination with an adjuvant. The most efficacious adjuvant was azathioprine followed by cyclophosphamide.[9] A multicenter randomized, placebo-controlled trial assessing the usefulness of mycophenolate mofetil in patients with mild to moderate disease severity found it to be only marginally effective with no advantage on the primary end point.[10] The use of mycophenolate mofetil is further limited by its high cost.

The major change in the therapeutics of pemphigus was the concept of pulse therapy introduced by Pasricha and Gupta.[5] As stated earlier, this regimen revolutionized pemphigus treatment in India. Later many modifications of DCP were introduced with good efficacy and reasonable safety.[6] We prefer DCP pulse therapy in patients with moderate to severe disease or patients with mild disease who fail conventional treatment and have no contraindication for pulse therapy. However, the major drawbacks of this regimen are the long treatment duration and lack of immunological monitoring. In a study to assess the need for continuing DCPs in the consolidation phase, we observed that the DCPs had no advantage over oral cyclophosphamide.[11] Patients could be shifted directly from phase I to phase III without increase in the relapse rate. We also found that periodic direct immunofluorescence (DIF) and enzyme-linked immunosorbent assay (ELISA) of desmoglein (Dsg) 1 and Dsg3 were useful in monitoring disease activity and to predict relapse.[11] In daily practice, it is advisable to assess the immunological activity by Dsg 1 and 3 index values (or DIF if facilities for ELISA are not available) 3 monthly in patients who are in clinical remission. Patients in clinical remission, but who are immunologically active have a higher chance of relapse if treatment is stopped prematurely. Oral cyclophosphamide, 50 mg once a day should be continued until both clinical and immunological remission is obtained. Thus, with a few modifications the duration of pulse therapy could be reduced by 9 months (by eliminating phase II) and relapse rate decreased (by immunological evaluation). In patients not suited for DCP therapy, some authors have used oral mini pulse, betamethasone 5mg on two consecutive days a week.[12] However, the data on the use of this regimen appears to be limited.

With the availability of novel targeted therapeutic agents, patients who fail DCP/conventional treatment, and those in whom they are contraindicated or cause severe adverse effects can now be offered IVIG and/or rituximab. IVIG alone or in combination with rituximab is preferred in patients with extensive disease in whom immediate control of disease activity is required. It can also be safely used in patients in sepsis or those who are at risk of infection. We had previously reported the efficacy of rituximab in an open label study with a complete remission rate of 70%.[13] In a randomized controlled, investigator blinded trial, we recently showed that better clinical and immunological outcomes are achieved in patients treated with two doses of 1000 mg rituximab in comparison with 500 mg doses.[14] Long term data on rituximab is now available, with a complete remission rate of 80-86% after a single infusion cycle.[15,16]

Though we are following a three tier approach, we offer rituximab treatment to all pemphigus patients irrespective of severity. Our own experience and evidence in the literature suggests that treatment with rituximab results in early remission, fewer relapses, and an overall better prognosis.[17] Many other authors also share the view of using rituximab as a first line therapy.[18-20] Ever since we started using rituximab in 2010 we were impressed by its efficacy. This was highlighted by us in an earlier editorial entitled "Rituximab in pemphigus" in this journal.[21] We are pleased to know that rituximab is also being used now at other centers in India. However, the major limitations of these agents in the Indian scenario are cost, availability, lack of expertise and limited clinical experience.

Although the cost of therapy with conventional drugs appears to be lower, the cost associated with complications of conventional therapies and their management is overlooked. Conventional treatment modalities require repeated hospital admissions and frequent hospital visits with subsequent loss of employment and income adding to the cost of therapy. A pharmacoeconomic study comparing the cost of treatment between IVIG and conventional drugs in autoimmune blistering diseases including pemphigus found that conventional treatment modalities had significant side effects, many of which were hazardous and required prolonged and frequent hospitalizations. Some of these side effects were severe enough to require discontinuation of treatment. The authors found that the mean total cost of treatment with IVIG therapy was statistically significantly less than that of conventional drugs and their complications during the entire course of the disease and on an annual basis.[22] With better clinical experience, wider acceptance of these targeted therapeutic agents may be seen in future and this may become first-line therapy.

Topical therapies are used as an adjuvant in the majority of patients, especially in the oral cavity. Various topical therapies including corticosteroids, cyclosporine, and tacrolimus have been described to be useful. Corticosteroid injections are commonly used and are considered to be the most effective topical treatment for oral pemphigus.[23] In an open label trial evaluating the role of perilesional/intralesional triamcinolone acetonide in the management of oral pemphigus, the authors found that patients treated with corticosteroid injections had earlier and higher rates of complete clinical remission and a lower total cumulative dose of oral corticosteroids.[24] Local hygiene is equally important since poor oral hygiene is associated with disease flare and persistence.

The often neglected drugs in pemphigus therapeutics are dapsone, and tetracycline and nicotinamide. They are specially useful in treating rare variants of pemphigus including pemphigus herpetiformis, IgA pemphigus and IgG/IgA pemphigus.[25] These subtypes respond dramatically to dapsone within days. They are also safe and require less vigorous monitoring than other adjuvants.

Certain special situations require mention in pemphigus therapeutics. Pregnancy and lactation severely limit the choice of treatment agents since commonly used cytotoxic drugs are contraindicated. Further, pemphigus *per se* can also lead to intrauterine growth restriction, premature delivery or death in addition to causing neonatal pemphigus.[26] Systemic corticosteroids are an important and safe therapeutic option in pregnancy. Unlike fluorinated corticosteroids, prednisone does not pass through the placenta and is the preferred choice.[27] It should preferably be given at doses less than 20 mg daily.[27] The other steroid sparing adjuvants that are relatively safe in pregnancy include azathioprine and IVIG.[28,29]

Pemphigus is rare in children and in our previous study, children aged less than 15 years accounted for 3.7% of all cases.[1] A recent review of the English literature found 33 cases of childhood pemphigus (aged <12 years) and 47 cases of juvenile pemphigus (aged 12-18 years).[30,31] Treatment modalities reported included systemic corticosteroids, azathioprine, dapsone, and IVIG.[30,31] We have used rituximab in 10 patients of childhood and juvenile pemphigus with a complete remission rate of 80%.[32] Though early reports are encouraging, more data is required on the long term safety of rituximab in childhood pemphigus.

Treating pemphigus is akin to walking a tightrope. The therapeutic efficacy of any drug has to be balanced against its potential toxicity and systemic immunosuppression. No individual drug is uniformly effective in all patients. Effective therapy for pemphigus lies in combining various agents to maximize efficacy and minimize side effects. Corticosteroids continue to play a central role in pemphigus therapeutics while we continue our search for safe and effective adjuvants.

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