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Review Article

An era of adjuvant therapies for oral pemphigus

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Abstract

Pemphigus vulgaris (PV) is an autoimmune disease characterized by blistering and erosions on skin and mucous membranes due to acantholysis. It is the second most common chronic bullous dermatosis; next to bullous pemphigoid. The use of corticosteroids since the 1950s has reduced the mortality from 60% - 90% to about 30%, but it still carries significant morbidity. The mainstay of treatment even today remains to be corticosteroids with or without other adjuvant therapies such as immunosuppressive agents, anti-inflammatory agents and immunomodulatory drugs. This paper emphasizes on popular adjuvant therapies that can help achieve long term remission even in case of recalcitrant lesions of pemphigus vulgaris.

Key words: Corticosteroid therapy, Pemphigus vulgaris

Introduction

The pemphigus diseases are a group of antibody-mediated disorders that manifest as blistering conditions of the skin and/or mucous membranes. Incidence of 0.1 to 0.5 cases per 100,000 persons per year worldwide with equal gender distribution[1].

The etiology and pathogenesis of PV are not completely clear, but there is a fairly strong genetic background: ethnic groups such as Ashkenazi Jews and people of Mediterranean and Indian origin are particularly susceptible and there is a link to HLA class II alleles. The initiating event in PV is not clear, but circulating IgG autoantibodies develop, directed particularly against the intercellular cadherin desmoglein 3 (Dsg3) in desmosomes of stratified squamous epithelium[2].

The measurement of Dsg 3-ELISA has been shown to be a sensitive and specific test for the diagnosis of PV in addition to the traditional indirect immunofluorescence autoantibodies titre[3] PV can be a serious, potentially fatal, disease with mortality approached 90% prior to the introduction of corticosteroids, and today it is approximately 10%[4]. Management is largely by systemic immunosuppressant with corticosteroids but newer treatments with potentially fewer adverse effects look promising.

Various Treatment Modalities

Before the 1950s the majority of patients with pemphigus died, usually from overwhelming sepsis, within one year of the onset of their disease. A clear and rapid fall in the mortality rate occurred after the introduction of corticosteroids in the 1950s[5] presently the morbidity is only 6%[6].

The main stay of treatment of pemphigus even though it is localized to the oral cavity is systemic corticosteroids. Oral lesions may respond to topical corticosteroids but some form of systemic immunosuppressant is required to tackle the circulating immune complexes.

Systemic corticosteroids

Systemic corticosteroids are the most useful drugs in the treatment of pemphigus vulgaris and continue to be the mainstay of therapy for this disease. Their use rapidly induces remission in the majority of patients but the clinician must weigh the benefits against the hazard from side effects of the drug[7].

Oral corticosteroids

The oral route of administration of corticosteroids is the one most preferred, and prednisone is the medication

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most frequently used.The initial dose of corticosteroid is usually 0.75 to 1 mg/kg/day, this dose may be increased by 25- 50% every 5-7 days if found insufficient in controlling the disease. The disease may be tentatively classified based on the severity of the lesion as mild, moderate and severe and can be treated at different levels based on this.

Bystryn[4] regimen recommends the following regimen

Mild disease is treated with a trial of topical corticosteroids, followed by low-dose (20 mg/day) oral steroids. About 50% of the patients receiving this treatment regimen are ultimately able to discontinue all therapy.Moderately severe pemphigus is managed with 60 – 80 mg/day of prednisone. For severe disease, the Bystryn regimen[8] recommends 80 mg of prednisone administered daily. If necessary, the dose is increased by 50% every 4 – 7 days until control is achieved, as demonstrated by the absence of new lesions and the disappearance of itching. This dose is maintained until there is 80 – 90% clearance of lesions. Reduction of the dose by 50% is recommended at two-week intervals.

Pulse therapy

The term pulse therapy refers to discontinuous or intermittent intra venous infusion of very high doses of drugs over a short period of time[9]. Among the many tried combination Dexamethasone-Cyclophosohamide pulse therapy has been promising as it's a combination of anti inflammatory and chemotherapeutic agent. Pasricha J S was the first person to use Dexamethasone-Cyclophosohamide pulse therapy for pemphigus in 1982[10]. All these drugs are given at high dose intravenously, it is said that the adverse effect profile of intravenous medication is less severe than that of oral therapy.

Each cycle consisted of a dosage of 100-136 mg of dexamethasone in combination with 500mg of cyclophosohamide, administerd as a slow infusion, over 3 consecutive days. These cycles have to be administered every 4 weeks. The adverse effect of pulse therapy is far less compared to conventional method of steroid therapy.

Combination Therapy

Therapy which combines corticosteroids and additional medications to control severe PV

This is utilized to minimize the adverse effects of prolonged steroid use and also to have steroid sparing effect. Combination therapy is currently gaining popularity even as the initial treatment of PV.

Cyclosporine

Cyclosporine (CsA) is a cyclic peptide composed of eleven amino acids (several are methylated on the peptidyl nitrogen). The drug is extracted from a soil fungus. CsA is used to prevent rejection of kidney, liver, and cardiac allogenic transplants. Although CsA can be used alone, it is more effective when glucocorticoids are also administered, and this is the usual practice. CsA is an alternative to methotrexate for the treatment of severe, active rheumatoid arthritis. Cyclosporine preferentially suppresses cell-mediated immune reactions, whereas humoral immunity is affected to a far lesser extent. Cyclosporine may be given either orally or by intravenous infusion. Oral absorption is variable. Many of the adverse effects caused by CsA are dose-dependent; therefore, it is important to monitor levels of the drug. Nephrotoxicity is the most common and important adverse effect of CsA. It is therefore critical to monitor kidney function[11].

Tacrolimus

Tacrolimus (TAC, originally called FK506) is a macrolide that is isolated from a soil fungus. Tacrolimus is approved for the prevention of rejection of liver and kidney transplants and is given with a glucocorticoid. This drug has found favor over CsA, not only because of its potency and decreased episodes of rejection but also because lower doses of glucocorticoid can be used, thus reducing the likelihood of steroid-associated adverse effects. TAC exerts its immunosuppressive effect in the same manner as CsA, except that it binds to a different immunophilin, FKBP-12 (FK-binding protein).

TAC may be administered orally or intravenously. The oral route is preferable, but as with CsA, oral absorption of TAC is incomplete and variable, requiring tailoring of doses. Absorption is decreased if the drug is taken with high-fat or high-carbohydrate meals. TAC is from 10- to 100-fold more potent than CsA. Nephrotoxicity and neurotoxicity (tremor, seizures, hallucinations) tend to be more severe in patients who are treated with TAC than in patients treated with CsA, but careful dose adjustment can minimize this problem. Coadministration with cyclosporine results in additive or synergistic nephrotoxicity; therefore, a delay of at least 24 hours is required when switching a patient from cyclosporin to tacrolimus[11].

Sirolimus

Sirolimus (SRL) is a recently approved macrolide obtained from fermentations of a soil mold. The earlier name-and one that is sometimes still used is rapamycin. It is equipotent to CsA. The drug is available only as oral preparations. Although it is readily absorbed, high-fat meals can decrease the drug's absorption. SRL is extensively bound to plasma proteins, and its immunosuppressive actions persist for six months after suspension of therapy. A frequent side effect of SRL is hyperlipidemia (elevated cholesterol and triacylglycerol), which can require treatment.

Azathioprine

Azathioprine has been the cornerstone of immunosuppressive therapy during the last several decades. It is a prodrug that is converted first to 6-mercaptopurine (6-MP), and then to the corresponding nucleotide, thioinosinic acid. The immunosuppressive effects of azathioprine are due to this nucleotide analog. In a long-term study by Aberer[12], 29 patients treated with combined steroid-azathioprine regimen were available for complete follow-up lasting 4 to 16 years. It was concluded that azathioprine-corticosteroid treatment of PV was effective and safe enabling long-term remissions in most patients and possibly to a cure in some. The side effects of azathioprine include bone marrow suppression, liver dysfunction and increased incidence of malignancy.

Mycophenolate mofetil

Azathioprine is being replaced by Mycophenolate mofetil because of the latter's safety. There were a number of recent studies showing favorable results in its use in PV. In one such study[13], with 12 patients who relapsed on steroid and azathioprine, MMF of 2 g/ day was kept for 12 months. Prednisolone 2 mg/kg was initiated and the dose was halved when new blistered ceased then tapered till below 5 mg/day. Eleven out of 12 patients were free of disease clinically within two months with no relapse during the follow up period of 12 months. The adverse effects of MMF are mainly gastrointestinal (diarrhoea, dyspepsia, abdominal pain, nausea), myelosuppressive and those due to immunosuppression. It has fewer toxic effects on liver compared to azathioprine. However, it is more expensive than the conventional immunosuppressive agents. Its use in the future is promising especially for the patient who cannot tolerate azathioprine or cyclophosphamide.

Methotrexate

The use of low dose methotrexate (10-17.5 mg/ week, mean 12.2 mg/week) was studied in nine patients[14]. They were also on prednisolone (3-40 mg/day, mean 20 mg/ day) and were unable to taper the dose for an average of 27 months before the study. Six patients were able to stop the systemic steroid within six months without a flare-up. However, all of them flared when methotrexate was stopped after an average of 23 days. It is obvious that, at some point, adjuncts in addition to methotrexate must also be used in these patients, since no patient in the study group experienced a complete remission on this regimen.

Anti-inflammatory agents

Dapsone was suggested to be an effective adjuvant to corticosteroids in PV[15]. Dapsone exhibits antibiotic effect, interferes with neutrophil chemotactic migration, reduces the release of prostaglandins and leukotrienes, inhibits neutrophil adherence to basement membranes,inhibits the generation of toxic radicals and protect cells from neutrophil- and eosinophil-mediated injuries. It does not stop the initial pathogenesis process but exhibits anti-inflammatory effects.[16] Some of the more common side effects of dapsone includes haemolysis, methaemoglobinaemia, neuropathy and allergic dermatitis.

Plasmapheresis

As the disease activity of PV generally correlates with the level of circulating autoantibodies, their removal seems a reasonable therapeutic approach. However, the use of plasmapheresis fails to control the rebound synthesis of antibodies due to a negative feedback mechanism. Pathogenic B cells are triggered with sudden drop in the circulating level of autoantibodies and secrete even more antibodies. The level of circulating antibodies was shown to increase as early as three hours after plasmapheresis. Therefore its utility on the long term management of oral pemphigus is questionable.

Conclusion

The chronicity and refractiveness of oral pemphigus is something that every clinician is aware of, inspite of the advances in medicine. Treatment goals remain the same; the suppression of circulating autoantibodies with use of corticosteroids and safer adjuvants. The use of adjuvant agents in treatment of PV is often limited by its potent adverse effects. The adjuvant therapy chosen should be individualized; the medical history of the patient, severity and course of the disease, possible side effects of the therapy and availability of resources are all important considerations.

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