Review on Pulse Therapy: A Novel Approach in the Treatment of Pemphigus Vulgaris

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ABSTRACT

Objective: Pemphigus vulgaris, a fatal autoimmune mucocutaneous disorder commonly seen involving the oral cavity, has since a long time remained a topic of concern regarding its treatment modalities. Pulse therapy, introduced in 1984, employs high-dose corticosteroids along with certain immunosuppressive agents and has gained wide popularity since the last three decades due to its advantage of minimizing the adverse effects of conventional corticosteroid therapy. This article provides a detailed review about various studies conducted utilizing different regimens in pulse therapy and the outcome of these studies.

Materials and methods: Information from various studies conducted over the last three decades was collected and a thorough analysis of the results of these studies has been provided in this article.

Results: Extensive review of the existing data revealed that pulse therapy minimizes the adverse effects of long-term corticosteroid therapy, controls the disease process faster and has quicker and long-lasting remission rates.

Conclusion: Pulse therapy appears to be successful in the treatment of pemphigus vulgaris. Various studies have proven the efficacy of pulse therapy along with reduced side effects of conventional corticosteroid therapy. However, long-term follow-up is necessary to compare the incidence of malignancy in patients receiving pulse doses of immunosuppressive agents with that in patients receiving continuous oral treatment.

Keywords: Pemphigus vulgaris, Corticosteroids, Pulse therapy, Cyclophosphamide, Azathioprine.

INTRODUCTION

Pemphigus vulgaris (PV) is a chronic autoimmune blistering disease of skin and mucous membrane.1 The demonstration by Beutner and Jordan of serum antibodies directed against the intercellular substance of stratified squamous epithelium was the first in a series of findings that suggested that PV may be an autoimmune disease.2 It is a potentially fatal disease with a mortality rate of 50% at 2 years, 100% at 5 years, if untreated.3

PATHOPHYSIOLOGY

PV is precipitated by IgG autoantibodies binding to desmoglein 3 (Dsg3) and desmoglein 1 (Dsg1).4,5 Antibodies to Dsg3 are associated with mucosal dominant pemphigus, whereas the presence of both Dsg3 and Dsg1 antibodies feature mucocutaneous pemphigus with lesions both in oral cavity and on the skin. The antigen-antibody reaction activates the complement system resulting in acantholysis and fluid accumulation forming the characteristic vesiculobullous lesions.6 The autoantibodies can be detected in the epithelium using direct immunofluorescent staining techniques, which reveal a characteristic “spider-web” distribution of reaction products. Circulating antibodies are detectable in 80%-90% of patients with PV, and the titer is generally correlated with the level of clinical disease.2,7

The current body of research argues that acantholysis in PV occurs as an active process resulting from intracellular signaling triggered as a result of immunoglobulin (IgG) binding to the keratinocyte membrane antigen in a receptor-ligand fashion.6 Recently, nondesmoglein autoantibodies to cholinergic receptors (human alpha 9 acetylcholine receptor) have also been found capable of inducing clinical features of PV. These receptors are thought to regulate adhesion and motility of keratinocytes. Their activation, hence brings about disassembly of desmosomes and acantholysis. Also, there is evidence regarding the role of TNF-α and interleukin-6 (IL-6) as mediators in the blistering process of PV.6

CLINICAL FEATURES

While there are various types of pemphigus such as vulgaris, foliaceus, vegetans and paraneoplastic, 80% of all patients with pemphigus have PV.7 It affects both sexes equally and is more common among Ashkenazic Jews. It is commonly seen in fifth to seventh decade of life though some pediatric cases have also been reported. Oral mucosa is affected in nearly all the cases and is the site of first lesion in majority of cases.7

DIAGNOSIS

The formation of trauma-induced bullae is one of the diagnostic tools: A positive Nikolsky's sign or Asboe-Hansen sign (Nikolsky's sign II) are indicative of mucocutaneous bullous disease, such as PV.3,7 However, the definitive diagnosis is not solely dependent on positive examination since many other oral vesiculo-bullous and ulcerative lesions like erosive lichen planus,
pemphigoid and erythema multiforme have a similar clinical appearance. Histological examination of PV on hematoxylin and eosin staining reveals intraepithelial clefs or bullae, acantholysis and a dense mononuclear lymphocytic infiltration. A smear taken from new lesion can also be used to identify acantholytic cells called “Tzanck cells”, which are indicative of PV. However, the identification of Tzanck cells is not diagnostic since these can also be found in herpes simplex, carcinoma and transient acantholytic dermatosis.7

TREATMENT

The initial aim of the treatment of PV is to control the disease and induce disease remission.6,8 In a study conducted among various Asian physicians treating cases of PV, the expert opinion regarding the definition of disease control was the development of no new lesions and healing most of the previous lesions.9 This should be followed by a period of maintenance treatment using the minimum drug doses required for disease control in order to minimize their side effects.5

Systemic corticosteroids are the most useful drugs for the treatment of PV, first used for this purpose by Thorn et al and popularized by Costello et al and Lever and White.10 Since their introduction, the mortality associated with PV has declined, and is now estimated to be 5 to 15%.5,11

Due to severe side effects like infection, thromboembolic phenomenon, gastrointestinal complications, osteoporosis, diabetes, psychological disorders, cardiovascular disorders, myopathy, etc. associated with their prolonged administration and high doses, there has been a considerable effort to find alternate methods of treatment.10,12 While serious and fatal complications of corticosteroid therapy may occur at any dosage, a marked increase in mortality and morbidity was noted with dosages greater than 120 mg of prednisolone daily.12

Various adjuvant therapies employed include immunesuppressive agents (cyclophosphamide, azathioprine), dapsone, cyclosporine, antimalarials, gold, monoclonal antibodies (rituximab, etanercept), intravenous immunoglobulins, cholinergic drugs, tetracyclines and their derivatives, immunomodulators (mycophenolate mofetil, tacrolimus), etc. Among various types of therapies used pulse therapy (PT) deserves a mention along with plasmapheresis, extracorporeal photochemotherapy and immunoadsorption.1, 6,10-12

PULSE THERAPY

Pulse therapy (PT) was first described by Pasricha and Ramji in 1984.3-6,8,13 It has been defined as discontinuous or intermittent intravenous infusion of very high doses (megadoses) of drugs over a short time.3,6,14,15 The theoretical aims of pulsing are to achieve more rapid and effective disease control compared with conventional oral dosing, thus allowing a reduction in long-term maintenance corticosteroid doses and their side effects.8

In PT, doses of each pulse are not standardized but are usually 10 to 20 mg per kilogram of body weight for methylprednisolone (250-1000 mg) and 2 to 5 mg per kilogram of body weight (50-200 mg) for dexamethasone. Single doses of 500 mg of methylprednisolone and 100 mg of dexamethasone are both considered equivalent to 625 mg of prednisone. These very high doses, sometimes termed megadoses, are usually given as intravenous infusions over 30 minutes to 1 hour daily or every other day for a total of 1 to 5 administrations. In most indications, pulse glucocorticoid therapy is accompanied and/or followed by the continuous administration of lower intermediate-dose glucocorticoids and/or immunesuppressive agents like cyclophosphamide and azathioprine.15

In 1982, Pasricha et al treated five patients suffering from PV with an arbitrarily designed regimen. The regimen consisted of giving 100 mg dexamethasone in 500 mL of 5% glucose by a slow intravenous infusion on three consecutive days, along with 500 mg cyclophosphamide on one day only. Such dexamethasone-cyclophosphamide pulses (DCP) were given once a month and in between these pulses the patients received only 50 mg cyclophosphamide orally per day. After having received a total of 14 to 48 DCPs, further treatment for PV was withdrawn (Table 1). All the patients were in continuous clinical remission for 4 to 9 years.16

In another study, 79 patients with PV were treated with an arbitrarily designed regimen of 100 mg dexamethasone dissolved in 5% glucose given by an intravenous infusion over 1 hour, daily on three consecutive days and in addition, 500 mg cyclophosphamide on day 1 only. The intermittent high doses (IHD) of dexamethasone were repeated every 2 to 4 weeks, and the patient continued to take 50 mg/day oral cyclophosphamide. This treatment was divided into four phases. During Phase I, the patient continued to develop relapses of PV a variable number of days after IHD, but the lesions healed up quickly after IHD. These relapses became progressively milder and stopped after a few months, but the IHD were continued once a month for 6-9 months (Phase II). In the next phase (Phase III), the monthly IHD were stopped, and the patient continued to take 50 mg/day cyclophosphamide orally (Table 1). After approximately 1 year, this maintenance treatment was withdrawn and the patient was observed for any relapses (Phase IV). It was found that only seven patient had active disease at the end of the study while majority had either attained remission or were just on maintenance doses. The remissions were found to be long lasting. Side-effects of corticosteroids and cyclophosphamide were minimal and not clinically significant except for increased susceptibility to infections.17

In their study on 50 patients with PV, Kaur et al used the DCP PT. The pulse consisted of 136 mg dexamethasone dissolved in 5% dextrose given in a drip over a period of 1 to 2 hours on 3 consecutive days. In addition, 500 mg cyclophosphamide was added in the drip on the first day. Such pulses were given at monthly intervals. In between the pulses, patients were given 50 mg cyclophosphamide orally each day (Table 1). The lesions were found to heal in 3 to 4 days time in majority of patients and the chief advantage found was freedom from side-effects of corticosteroids.18

In another study, it was found that the patients responded well to monthly doses of intravenous cyclophosphamide with rapid decrease in the frequency and severity of blistering resulting in resolution of their disease after 7 to 10 months (Table 1). In their study, Chryssomallis and coworkers treated eight patients with PV alternate-day, one hour, infusions of 8, 9 or
10 mg/kg methylprednisolone Na succinate. Oral prednisone and a second immunosuppressive agent were simultaneously administered. These were rapidly decreased when control of the disease was achieved (Table 1). They found that all the patients initially responded well to therapy but the disease recurred in four patients after 3, 4, 9, and 16 months of remission, respectively. Three of these patients were treated again with PT and went into remission. None of the patients who received cyclophosphamide had a recurrence.20

In a retrospective, case-controlled study, Wreth et al included 15 patients with PV dividing them into two groups—one group received very high-dose intravenous pulses of methylprednisolone sodium succinate and the other did not receive intravenous PT (Table 1). In this study, patients treated with PT and control patients treated with conventional oral prednisone had similar initial disease severity. Six of the nine patients who received PT showed improvement of their PV. Therapeutic benefit was seen in patients who received PT early or late after beginning glucocorticoid therapy. In contrast, none of the six control patients has achieved long-term remissions without therapy. Hence, they concluded that patients treated with conventional orally administered doses of prednisone had protracted courses requiring years of glucocorticoid therapy with no long-term remissions.21

In their study on 123 patients with PV, Dadras and coworkers divided the patients into two groups—one group received pulse therapy with methylprednisolone within three consecutive monthly doses (1000 mg intravenous methylprednisolone for four days plus 500 mg intravenous cyclophosphamide for one day) and the second group where the patients received 1 to 2 mg/kg/day oral prednisolone for 28 days plus 1.5 mg/kg/day azathioprine. They found that PT with methylprednisolone-cyclophosphamide was generally well tolerated, safe and associated with lesser side effects.23

In a study, DCP was used to treat 20 patients with bullous dermatoses, including six with PV. On each of days 1 to 3, 100 mg dexamethasone was administered intravenously and on day 1, 500 mg cyclophosphamide IV. In the therapy interval between the pulses 50 mg cyclophosphamide per day was administered. Initially the pulses were repeated every two weeks and later at 10-week intervals (Table 1). After six months of this regimen, 13 patients were symptom-free, 4 had improved, and 3 showed no change. They concluded that DCP PT appears to be a good alternative to the standard continuous corticosteroid treatment.22

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Recently, a variant of pulse therapy has been proposed for patients with significant corticosteroid related toxicity and unresponsiveness to multiple immunosuppressive adjunctive therapies. Here, cyclophosphamide is given intravenously at the dosage of 50 mg/kg/day for four consecutive days and followed by the administration of granulocyte-colony stimulating factor (G-CSF), 5 μg/kg/day, beginning six days after last day of cyclophosphamide until the absolute neutrophil count exceeds 1000/ mm³. Febrile neutropenia and sepsis are common side effects of this immunoablative therapy.3

### SIDE-EFFECTS OF PULSE THERAPY

Cyclophosphamide, an alkylating agent is one of the most potent chemical immunosuppressants available and used as an adjuvant in PT. It induces a decrease in cellularity of lymphoid organs in

<table>
<thead>
<tr>
<th>Sl. no</th>
<th>Researchers</th>
<th>Year in which reported</th>
<th>Number of patients treated</th>
<th>Regimen used</th>
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<tbody>
<tr>
<td>1</td>
<td>Pandya AG, Sontheimer RD20</td>
<td>1992</td>
<td>2</td>
<td>IV cyclophosphamide</td>
</tr>
<tr>
<td>2</td>
<td>Appelhans M, Bonsmann G, Orge C, Brocker EB22</td>
<td>1993</td>
<td>20</td>
<td>100 mg dexamethasone IV on days 1 to 3 with 500 mg cyclophosphamide IV on day 1 along with 50 mg/day oral cyclophosphamide. PT repeated initially every 2 weeks and then at 10 weeks interval. Total duration of treatment was 6 months.</td>
</tr>
<tr>
<td>3</td>
<td>Chryssomallis F, Dimitriades A, Chaidemenos GC, Panagiotides D, Karakatsanis G20</td>
<td>1995</td>
<td>8</td>
<td>Alternate day 1 hour infusion of 8, 9 or 10 mg/kg methylprednisolone sodium succinate along with oral prednisolone and cyclophosphamide.</td>
</tr>
<tr>
<td>4</td>
<td>Wreth VP21</td>
<td>1996</td>
<td>15</td>
<td>High dose IV methylprednisone sodium succinate.</td>
</tr>
<tr>
<td>5</td>
<td>Pasricha JS, Thanzama J, Khan UK17</td>
<td>2006</td>
<td>79</td>
<td>100 mg dexamethasone in 5% glucose by IV infusion over 1 hour daily on 3 consecutive days along with 500 mg cyclophosphamide IV on day 1 only plus 50 mg oral cyclophosphamide. Doses of dexamethasone repeated at 2 to 4 weeks.</td>
</tr>
<tr>
<td>6</td>
<td>Kaur S, Kanwar AJ18</td>
<td>2007</td>
<td>50</td>
<td>136 mg dexamethasone in 5% dextrose drip 1 to 2 hours on three consecutive days along with 500 mg cyclophosphamide added to the drip on day 1 given at monthly intervals plus 50 mg oral cyclophosphamide.</td>
</tr>
<tr>
<td>7</td>
<td>Pasricha JS, Das SS16</td>
<td>2007</td>
<td>5</td>
<td>100 mg dexamethasone in 500 ml of glucose slow IV infusion on three consecutive days along with 500 mg cyclophosphamide on day 1 only. DCP given once a month only 50 mg oral cyclophosphamide is continued. Total of 14 to 18 DCP pulses are given.</td>
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low doses, while not affecting hematopoietic cells. At high doses, it is selectively toxic for B-lymphocytes with regenerating B-lymphocytes being much more sensitive than resting B-lymphocytes. As an adjuvant in PT, it may prevent the disease from recurring. However, some studies have found a risk of cardiac arrest with its prolonged use. The risk of cardiac arrest exists even with less aggressive form of PT. A medical history of supraventricular arrhythmias may be considered a risk factor. Also, myelosuppression, gonadal damage, teratogenicity, hemorrhagic cystitis, leukopenia and reversible alopecia are other side-effects associated with the use of cyclophosphamide. Cummins et al. found adverse effects like hematuria, nonlife-threatening infections and transitional cell carcinoma of urinary bladder as the adverse effects associated with its use. Though, there were no deaths reported with its use, they recommended close monitoring of the patients on cyclophosphamide.

Pandya et al. have recommended a pulse cyclophosphamide protocol to be followed in using this drug as a constituent of PT. They have suggested that the intermittent high-dose protocol with cyclophosphamide impairs immune surveillance for relatively short periods of time compared with daily oral therapy. Therefore, the malignant potential using this protocol may be less than those using standard doses. Good hydration is extremely important in protecting the bladder when giving cyclophosphamide both orally and intravenously. It has been reported that concomitant pulse-cyclophosphamide and corticosteroid lead to complete remission in 37% and mortality in 3% of cases.

Azathioprine, another commonly used immunosuppressant and adjuvant in PT has been associated with side effects like myelosuppression, nausea, hepatotoxicity, hypersensitivity reactions and increased susceptibility to infections. Skin cancer and lymphoma after long-term use of azathioprine have been reported in renal transplant patients. Reports suggest slow steroid sparing action as compared to cyclophosphamide, complete remission rates of 28 to 45% and mortality rates of 1.4 to 7% associated with the use of azathioprine.

CONCLUSION
PT appears to be successful in the treatment of PV. High-dose steroid therapy can be tapered with the use of this treatment. Various studies have proven the efficacy of pulse therapy along with reduced side-effects of conventional corticosteroid therapy. However, long-term follow-up is necessary to compare the incidence of malignancy in patients receiving pulse doses of immunosuppressive agents with that in patients receiving continuous oral treatment.

REFERENCES