Review Article

# Pulse therapy: Opening new vistas in treatment of pemphigus

**Subhasish Mustafi[1], Rupam Sinha[1], Samhita Hore[1], Suman Sen[1], Subhadeep Maity[1], Pritha Ghosh[1]**

*[1]Department of Oral Medicine and Radiology, Haldia Institute of Dental Sciences and Research, HIDSAR Campus, Banbishnupur, Balughata, Purba Medinipur, West Bengal, India*

## Abstract

Pemphigus is comprised of a group of life-threatening autoimmune diseases that is characterized by circulating IgG antibodies targeting several types of keratinocyte antigens. After introduction of systemic steroids, survival has improved dramatically. However, mortality and morbidity were still very high due to side effects of steroids. Pulse therapy is defined as discontinuous/intermittent intravenous infusion of very high doses of corticosteroids along with certain immunosuppressive agents over a short period. This therapy was introduced to minimize the side effects of conventional corticosteroid therapy. The target is to achieve a faster response and stronger efficacy and to decrease the need for long-term use of systemic corticosteroids. As a result, this therapy has gained its popularity since three decades. The purpose of this article is to review the various available pulse therapy regimens with dosage, indications and contraindications and side effects.

**Keywords:** Corticosteroids, immunosuppressive agents, pemphigus, pulse therapy

Pemphigus is comprised of a group of a life-threatening autoimmune diseases that is characterized by circulating IgG antibodies targeting several types of keratinocyte antigens.[1-3] The term pemphigus was derived from the Greek word Pemphix, meaning bubble or blister, introduced by Hippocrates (460-370 BC), who described a pemphigoid fever as "pemphigodes pyertoi," a disease that was not having blisters and accordingly perhaps did not signify pemphigus. Galen (AD 13 1-201) named a pustular disease of the mouth as "febris pemphigodes." Zacutus, a Jewish physician again used the term "febris pemphigodes" in 1673 to describe patients with blisters of short duration. The term pemphigus was originally given by Wichmann in 1791, who classified the disease as a chronic bullous disease. Pemphigus vulgaris (PV) was recognized as a separate entity by Lever in 1953, based on its clinical aspects, natural course and histopathology.

**Address for correspondence:** Dr. Subhasish Mustafi, F-34/4, Karunamoyee Housing Estate, Salt-lake City, Sector-2, Kolkata - 700 091, West Bengal, India.
E-mail: subhasish2632@gmail.com

**Access this article online**

Quick Response Code:

Website: www.jfmpc.com

DOI: 10.4103/jfmpc.jfmpc_114_19

Pemphigus is a category of chronic mucocutaneous blistering diseases. It is caused by autoantibodies directed against the desmosomal cadherins desmoglein (Dsg1) and/or (Dsg3).[4]

Pemphigus has a worldwide incidence of 0.76–5 cases per 1,000,000 per year.[5] The incidence of different subtypes of pemphigus varies from country to country. Pemphigus vulgaris (PV) and the sporadic form of pemphigus foliaceus (PF) are most common in Europe and the USA. The incidence of PF in these countries is about a fifth to a tenth of that of PV.[6] Endemic PF is frequently diagnosed in rural areas of Brazil and other underdeveloped areas of the world.[7] Pemphigus affects all races but is diagnosed more often in people of Ashkenazi Jewish, Greek, and Indian descent.

Pemphigus can be divided into two major forms, based on the level of the blistering in the epidermis: Pemphigus Foliaceous (PF) and Pemphigus Vulgaris (PV) [Table 1].



**How to cite this article:** Mustafi S, Sinha R, Hore S, Sen S, Maity S, Ghosh P. Pulse therapy: Opening new vistas in treatment of pemphigus. J Family Med Prim Care 2019;8:793-8.

**Table 1: Main types of pemphigus involving the oral mucosa includes[8]**

| Variant | Oral lesions | Antigen localization | Target Antigens | Antibody Class |
|---|---|---|---|---|
| Mucosal PV | Common | Desmosomes | Dsg3 | IgG |
| Muco-cutaneous PV | Common | Desmosomes | Dsg3& Dsg1 | IgG |
| IgA pemphigus | Common | Desmosomes | Dsg3<br>Desmocollin 1<br>Desmocollin 2 | IgA |
| Paraneoplastic pemphigus | Common | Desmosomes or Hemidesmosomes | Desmoplakin 1<br>Desmoplakin 2<br>Periplakin<br>BP230 | IgG or Ig A |
| Pemphigus foliaceus | Uncommon | Desmosomes | Dsg1 | IgG |

Because pemphigus includes a group of a life-threatening autoimmune diseases, patients require extensive health education in terms of their responsibility in managing their condition. The purpose of this article is to review the various available pulse therapy regimens with dosage, indications, contraindications, and its side effect. The content of this article will give a clear idea to the family physicians regarding "Pulse Therapy" so that they can implement it while managing patients suffering from pemphigus diseases.

Pemphigus Vulgaris is a chronic autoimmune blistering disease of skin and mucous membrane. Prior to the advent of corticosteroids, the majority of patients with Pemphigus Vulgaris died from overwhelming sepsis. After introduction of systemic steroids, survival has improved dramatically. However, mortality and morbidity were still very high due to side effects of steroids. Steroid sparing agents like Azathioprine, Cyclophosmamide, Gold, Dapsone, Methotrexate were also used to the treatment of Pemphigus Vulgaris to reduce the high morbidity associated with long term use of oral steroids. However, these treatment modalities may cause adverse reactions of their own.[9]

To counter act these drawbacks, pulse therapy was introduced in treatment of pemphigus. Pulse therapy refers to the administration of a drug intermittently to accelerate the therapeutic efficacy. In other words pulse therapy refers to intravenous infusion of high dose of steroids for one or more days for quicker, better efficacy and to decrease the side effects of long-term steroids.[10-12]

Kountz and Cohn first successfully used pulse administration of Corticosteroids for treatment renal graft rejection. Pulse therapy using a combination of Corticosteroids and Cyclophosphamide for a blistering disorder in pemphigus vulgaris was first introduced by Pasricha *et al.* and by Kanwar at the All India Institute of Medical Sciences (AIIMS), New Delhi, in 1986.[13] Since then pulse therapy is been commonly used to treat various other diseases like systemic sclerosis, systemic lupus erythematosus, dermatomyositis, pyoderma gangrenosum, toxic epidermal necrolysis, Steven Johnson's syndrome, lichen planus, alopecia areata, sarcoidosis, and systemic vasculitis.[14]

## Phases of Pulse Therapy

### Dexamethasone cyclophosphamide pulse (DCP) therapy

The DCP therapy is divided in four phases.[15]

Phase I therapy includes administration of 100 mg of dexamethasone dissolved in 500 ml of 5% glucose as a slow intravenous drip over 2 hours repeated on 3 consecutive days. On the 2nd day, the patient is also given 500 mg of Inj. Cyclophosphamide in 500 ml of 5% Dextrose. This constitutes 1 DCP. Such DCPs are repeated at exactly 28-day intervals counted from the 1st day of the pulse. In between the DCPs the patient receives only 50 mg of Cyclophosphamide orally/day. The DCP regimen is administered in four phases.

During the phase I period in addition with DCP therapy 40–60 mg of prednisolone/day orally is given to achieve remission which is defined as complete healing of the existing lesions and absence of new lesions.

In case of phase II therapy, the patient remains completely alright clinically but receives 9 more DCPs at exactly 28-day cycles along with 50 mg Cyclophosphamide orally.

Phase III therapy is composed of complete withdrawal of DCP. During this phase patient receives only 50 mg Cyclophosphamide orally/day for the next 9 months.

Phase IV therapy includes stoppage of all treatment of pemphigus and the patient is followed up for the next 10 years to look for a relapse, if any.

### Objectives of DCP therapy

- To gain greater efficacy of the drug and fast response
- To avoid the need for long-term use of systemic steroids
- To achieve a steroid sparing effect.[16]

### Purpose of using glucocorticoids in case of pulse therapy

Glucocorticoids act by 2 mechanisms on cells. One is through low concentration that is through genomic effect and another

through high concentration that is through non-genomic effect.

At low concentration—Genomic effect

Glucocorticoids act by binding to the intracellular glucocorticoid receptor (GCR) which results in formation of GCR complex which activates the mitogen-activated protein kinase (MAPK) signaling pathway. This process leads to dimer formation and subsequent binding to specific DNA regulatory sequences known as GLUCOCORTICOID RESPONSE ELEMENTS (GREs), which results in anti-inflammatory and immunosuppressive effect by upregulation or down regulation of specific genes that encode for proteins, such as many cytokines and adhesion molecules.[17]

At high concentration—Non-genomic effect

Glucocorticoids exert their effects by non-genomic mechanism such as membrane bound receptors or physiochemical interaction with cellular membranes resulting in rapid immunosuppression via apoptosis and induction of lipomodulin. There are also post transcriptional effects of Glucocorticoids which include effects on RNA translation, protein synthesis, and secretion. End result of all these many effects is that Glucocorticoids inhibit the access of inflammatory cells to the tissues, interfere with function of fibroblasts and endothelial cells and suppress production and effects of humoral factors.[17]

## Cyclophosphamide

Cyclophosphamide is an alkylating agent which was first synthesized as a derivate of nitrogen mustard. It is used as an immunosuppressant in the treatment of various autoimmune disorders. Cyclophosphamide is primarily metabolized by the liver. It is a PRODRUG which gets activated in the liver by conversion through cytochrome P450 to 4-hydroxy cyclophosphamide. Its immunosuppressive properties are due to the metabolite Chloracetaldehyde produced after side chain oxidation of Cyclophosphamide. Oral Bioavailability is 74%. Peak Plasma levels occur within 1 hour. It is widely distributed throughout the body including cerebrospinal fluid. The half-life of the drug ranges from 2 to 10 hours.[18] Hepatic metabolisms is the principal route of elimination of Cyclophosphamide. Seventy percent of the drug is excreted in the urine as inactive compounds. As because the clearance of the active metabolites occurs by spontaneous degradation rather than renal excretion, renal failure does not influence toxicity directly.[19]

### Mode of action

Cyclophosphamide is an alkylating agent. It has the ability to form strong electrophiles that form covalent linkages to electron rich groups of DNA. The active metabolite is phosphoramide mustard, which undergoes cyclization to the reactive aziridium intermediate, which in turn alkalizes the DNA. The result is irreparable damage to the DNA and subsequent apoptosis of the cell. Cyclophosphamide although highly toxic to the rapidly dividing cells is different from several other cytotoxic agents in that it is toxic to the cells in all phases of the cell cycle.[20]

### Adverse effects

#### *Hematological toxicity*

Bone marrow suppression. Decrease in leucocyte count. Thrombocytopenia occurs less frequently.

Gonadal toxicity—In case of males; decrease in sperm count and in females it causes disappearance of primordial ovarian follicles.[21]

#### *Urological damage*

Cyclophosphamide causes increased frequency, dysuria, urgency, microscopic haematuria, hemorrhagic cystitis, fibrosis of bladder, and bladder necrosis.

#### *Carcinogenesis*

Cyclophosphamide is linked to squamous cell carcinoma of may be the bladder, urinary tract, and carcinoma of the renal pelvis and ureter.

## Modifications to Standard DCP Regimen[13]

- Superadded fungal infections must be controlled by proper usage of antifungal drugs and antibiotics
- Patient is advised to go for thorough cleaning of skin and scalp with soap and shampoo and maintenance of oral hygiene
- In case of critical situations intermittent pulse may be given fortnightly
- When Cyclophosphamide 500 mg was added to the drip on the second day of DCP, it was followed by an additional 5% dextrose of 500 ml, to prevent the urinary complications of Cyclophosphamide
- As part of the protocol, the following supportive drugs were given to all patients: oral calcium 500 mg daily, during the first 3 phases, and Inj. Vitamin D 3 lakh units once a month during the first 2 phases
- Patients with oral lesions were encouraged to clean the oral cavity with regular brushing of the teeth. They were advised to massage a topical corticosteroid gel on the oral ulcers three to four times a day especially after meals and given ketoconazole 200 mg/day orally and 500 mg Ciprofloxacin or Cefadroxil twice daily. This change leads to the healing of oral lesions within 2–3 months
- Earlier patients received only monthly pulses of corticosteroids, but with the observation many patients developed some degree of recurrence of lesions between the pulses in the early stages of therapy, daily corticosteroids were added in the 1st few months. Patients with extensive active disease were also given interval pulses of dexamethasone.[22]

## Other Pulse Therapies for Pemphigus

1. Dexamethasone Azathioprine Pulse (DAP): Here cyclophosphamide is replaced with 50 mg of Azathioprine daily during the 1st 3 phases. No bolus dose of Azathioprine is given during the pulse. This regimen is a viable option for patients who are unmarried or have not completed their family[10]
2. Dexamethasone Methotrexate Pulse (DMP): Here Cyclophosphamide is replaced by 7.5 mg of Methotrexate (3 doses of Methotrexate 2.5 mg at 12 hourly intervals) weekly given orally during the 1st 3 phases of pulse therapy[10]
3. According to rheumatoid arthritis Rituximab is also given for pemphigus as two doses of 1 g, 2 weeks apart and according to lymphoma protocol as 375 mg/m$^2$ weekly for 4 weeks.[10,23,24]

## Adverse Effects of DCP Therapy

The adverse effects of pulse therapy can be due to the constituents of the pulse or due to the pulse itself and are subdivided as follows:

### Due to corticosteroids

- Viral, bacteria, and fungal infections
- Hyperacidity
- Diabetes mellitus
- Hypertension
- Demineralization of bone/Avascular necrosis
- Spontaneous rupture of the Achilles tendon.[25]

### Due to cyclophosphamide

- Leucopenia
- Thrombocytopenia
- Diffuse loss of hair
- Diffuse hyper-pigmentation of skin and hyperpigmented bands in nails
- Hemorrhagic cystitis
- Gonadal damage
- Carcinogenesis.[26]

### Due to pulse therapy[10]

- Hiccups
- Facial flushing
- Weakness
- Metallic taste
- Muscle and bone pain
- Generalized swelling
- Diarrhea
- GI bleeding
- Headache
- Loss of taste
- Menstrual irregularities
- Hair loss
- Sleep disturbances
- Palpitations
- Hypotension
- Arrhythmias
- Congestive cardiac failure
- Pulmonary oedema
- Ischemic heart disease
- Sudden death
- Acute psychosis
- Seizure
- Anaphylaxis.

The most common side effects are

- Flushing
- Palpitations
- Weakness
- Menstrual irregularities
- Bad taste/Diarrhea
- Headache
- Sleep disturbances
- Polyurea
- Acute cardiovascular complication
- Infections.

## Precautions to be Taken before Administration of Pulse Therapy

### Before each pulse

- Patient should be free from systemic infections
- Control of blood pressure
- Complete blood count, urine analysis, electrocardiogram, renal function tests, liver function tests, serum electrolytes should be routinely done
- Cardiac assessment is required for elderly patients.[10]

### During and after therapy

- Pulse rate, respiratory rate and blood pressure must be monitored every 15—30 minute.
- Infusion must be discontinued in case of precipitation of an arrythmia
- Routine checkup of blood sugar level and electrolytes is required.[10]

## Controversies of Pulse Therapy

Though pulse therapy revolutionized the treatment for pemphigus but there are studies which has shown controversies related to this therapy also.

Singh *et al.* in 2009 conducted a study and minutely analyzed Pasricha' methodology of pulse therapy for treatment of pemphigus. Through their study they found that hyperglycemia is precipitated in case of diabetic patients when pulse therapy was given along with 5% glucose.[27]

Raman contraindicated the usage of cyclophosphamide in case of unmarried individuals and those who have not completed

their families for treatment of pemphigus as because in his study he found that when those people were given 50 mg cyclophosphamide daily resulted in gonadal failure even at a cumulative dose of 30 g and 12 g in women and men, respectively. He also found that pemphigus is aggravated due to prolong use of antibiotics like cephalosporin. Thus, he stated that antibiotics should be used until the infection clears and not until lesions heal.[28]

Setthy P K *et al.* in 2009 conducted a study to compare the efficacy and side-effects of dexamethasone cyclophosphamide pulse and daily oral cyclophosphamide (DCP + C) versus cyclophosphamide pulse and daily oral prednisolone (CP + P) in PV. 28 pemphigus patients were randomly chosen and DCP with daily oral cyclophosphamide or CP with tapering doses of daily oral prednisolone was administered in them for 12 months and they were followed-up for at least 3 months after stopping the therapy. A comparison was made among those patients for time taken to achieve mucocutaneous disease control, achieve remission, relapse during treatment period, relapse after stopping therapy, and side-effects. Of the 28 patients, 25 patients completed their study period and were analyzed. The result of their study showed early remission in case of CP + P usage, but relapse rates and side effects were comparable for both groups.[26]

Shahidi-Dadrason M *et al.* in 2007 conducted a study to compare the effectiveness and side-effects of oral and pulse steroid therapy in the treatment of pemphigus vulgaris. Totally, 123 patients with pemphigus vulgaris were included in this study and they were categorized into two groups of study and control according to the disease severity and patient's preferred method of treatment. The study group comprised of 36 males and 36 females. The control group comprised of 26 males and 25 females. During the induction phase, the study group was subjected to pulse therapy with methylprednisolone in 3 consecutive monthly courses. Each course comprised of 1000 mg intravenous methylprednisolone for 4 days plus 500 mg intravenous cyclophosphamide for 1 day. In this phase, the control group received 1-2 mg/kg/day oral prednisolone for 28 days plus 1.5 mg/kg/day azathioprine. All patients were followed for at least 12 months during which period, clinical response, relapse rate, and side-effects were evaluated. The result of their study showed no difference between the two groups in terms of therapeutic responses, remission, relapse, and complications.[29]

## Financial support and sponsorship

Nil.

## Conflicts of interest

There are no conflicts of interest.

## References

1. Grando SA. Pemphigus autoimmunity: Hypotheses and realities. Autoimmunity 2012;45:7-35.
2. Londhe PJ, Kalyanpad Y, Khopkar US. Intermediate doses of rituximab used as adjuvant therapy in refractory pemphigus. Indian J Dermatol Venereol Leprol 2014;80:300-5.
3. Varala S, Malkud S, Arakkal GK, Siddavaram D. Outcome of pulse therapy in pemphigus: A 10-year study. Clin Dermatol Rev 2018;2:69-73.
4. Lever WF. Pemphigus. Medicine (Baltimore) 1953;32:1-123.
5. Michel B, Ko CS. An organ culture model for the study of pemphigus acantholysis. Br J Dermatol 1977;96:295-302.
6. Wilgram GF, Caulfield JB, Lever WF. An electron microscopic study of acanthoysis in pemphigus vulgaris. J Invest Dermatol 1961;36:373-82.
7. Hashimoto K, Lever WF. An ultrastructural study of cell junctions in pemphigus vulgaris. Arch Dermatol 1970;101:287-98.
8. Scully C, Mignogna M. Oral mucosal disease: pemphigus. Br J Oral Maxillofac Surg 2008;46:272-7.
9. Fleischli ME, Vlaek RH, Pandya AG. Pulse intravenous cyclophosmamide therapy in pemphigus. Arch Dermatol 1999;135:57-61.
10. Abraham A, Roga G, Job AM. Pulse therapy in pemphigus: Ready reckoner. Indian J Dermatol 2016;61:314-7.
11. Panat SR, Aggarwal A, Joshi A. Pulse therapy: A boon or bane. J Dent Sci Oral Rehabil 2012;3:1-3.
12. Tarani S. Pulse therapy: A decisive treatment modality in dermatological disorders. Indian J Appl Res 2016;6:26-9.
13. Rao PN, Lakshmi TSS. Pulse therapy and its modifications in pemphigus: A six year study. Indian J Dermatol Venereol Leprol 2003;69:329-3.
14. Mittal R, Sudha R, Murugan S, Adikrishnan, Shobana S, Anandan S. Pulse therapy in dermatology. Sri Ramachandra J Med 2007; 1(2):144-6.
15. Pasricha JS, Poonam. Current regimen of pulse therapy for pemphigus: Minor modifications, improved results. Indian J Dermatol Venereol Leprol 2008;74:217-21.
16. Buttgereit F, da Silva JA, Boers M, Burmester GR, Cutolo M, Jacobs J, *et al.* Standardised nomenclature for glucocorticoid dosages and glucocorticoid treatment regimens: Current questions and tentative answers in rheumatology. Ann Rheum Dis 2002;61:718-22.
17. Buttgereit F, Saag KG, Cutolo M, da Silva JA, Bijlsma JW. The molecular basis for the effectiveness, toxicity, and resistance to glucocorticoids: Focus on the treatment of rheumatoid arthritis. Scand J Rheumatol 2005;34:14-21.
18. Ahmed AR, Hombal SM. Cyclophosphamide: A review on relevant pharmacology and clinical uses. J Am Acad Dermatol 1984;11:1115-26.
19. Fox LP.Pandya AG. Pulse intravenous cyclophosphamide therapy for dermatologic disorders. Dermatol Clin 2000:18:459-73.
20. Ho V, Zloty D. Immunosupressive agents in dermatology. Dermatol Clin 1993;11:73-85.
21. Hassan I, Sameem F, Masood QM, Majid I, Abdullah Z, Ahmad QM. Non comparative study on various pulse regimens (DCP, DAP and DMP) in pemphigus: Our experience. Indian J Dermatol 2014;59:30-4.
22. Kanwar AJ, Kaur S. Long term efficacy of Dexamethasone Cyclophosphamide Pulse Therapy in Pemphigus. Dermatology 2002:204:228-31.

23. Kanwar AJ, Vinay K. Rituximab in pemphigus. Indian J Dermatol Venereol Leprol 2012;78:671-6.
24. Longui CA. Glucocorticoid therapy: Minimizing side effects. J Pediatr (Rio J) 2007;83(Suppl 5):S163-71.
25. Sethy PK, Khandpur S, Sharma VK. Randomized open comparative trial of dexamethasone-cyclophosphamide pulse and daily oral cyclophosphamide versus cyclophosphamide pulse and daily oral prednisolone in pemphigus vulgaris. Indian J Dermatol Venereol Leprol 2009;75:476-82.
26. Sethy PK, Khandpur S, Sharma VK. Randomized open comparative trial of dexamethasone-cyclophosphamide pulse and daily oral cyclophosphamide versus cyclophosphamide pulse and daily oral prednisolone in pemphigus vulgaris. Indian J Dermatol Venereol Leprol 2009;75:476-82.
27. Singh S, Chaudhary R. Pulse therapy for pemphigus: The burden of proof. Indian J Dermatol Venereol Leprol 2009;75:82-4.
28. Ramam M. Prolonged antimicrobial and oral cyclophosphamide therapy in pemphigus: Need for caution. Indian J Dermatol Venereol Leprol 2009;75:85.
29. Shahidi-Dadras M, Karami A, Toosy P, Shafiyan A. Pulse versus oral methylprednisolone therapy in pemphigus vulgaris. Arch Iran Med 2007;10:1-6.