Pulse therapy as a cure for autoimmune diseases

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Pulse therapy means the administration of large (supra-pharmacologic) doses of drugs in an intermittent manner to enhance the therapeutic effect and reduce the side effects.[1-3]

The first reported use of pulse administration of corticosteroids is attributed to Kountz and Cohn[4] who used it to successfully prevent renal graft rejection. Subsequently, pulse doses of corticosteroids were used for several other diseases such as lupus nephritis, rheumatoid arthritis and pyoderma gangrenosum,[5-7] but usually to deal with emergency situations only and not as a preferred method of treatment. Methylprednisolone was the commonest drug used, in a dose of 1 g per dose for a variable number of days.

We first used pulse therapy in a patient having Reiter's disease and could save him from an almost certain death.[8] Continued use of pulses at 1 month intervals led him to a remarkable recovery and a fairly useful life for the next 10 years. For pemphigus, the pulse therapy was first used by us in 1982,[9] for systemic sclerosis in 1989,[10] for pyoderma gangrenosum in 1990,[11] and other diseases in subsequent years.[1] However, we used 100 mg dexamethasone on three consecutive days at 4 week intervals and continued to use the pulses for a specified period even after the patient had recovered from the disease completely. This was done to ensure that the patient would not develop a relapse in future. By now we have used pulse therapy for more than 1000 patients having pemphigus, 100 cases of systemic sclerosis, 25 patients having systemic lupus erythematosus, 20 patients having dermatomyositis, 10 patients having pyoderma gangrenosum and fewer cases of other diseases including extensive lichen planus, prurigo nodularis, generalized morphea, DLE, scleredema, recurrent alopecia universalis, extensive vitiligo, allergic vasculitis, disseminated porokeratosis, Darier's disease, Hailey-Hailey disease, multiple keloids, sarcoidosis, multicentric histiocytosis, and Peyronie's disease with similar success. With this experience over the last nearly 20 years, it seems logical to claim that it is now possible to cure almost all the autoimmune and several other corticosteroid responsive dermatoses and avoid the side effects commonly associated with the conventional daily-dose regimens of corticosteroid administration. To achieve optimum results it is important to strictly follow the regimen recommended by us in all its details. Any compromises have produced inferior results.

THE REGIMEN

The pulse therapy regimen designed by us is called the DCP regimen or the dexamethasone-cyclophosphamide pulse (DCP) therapy regimen. In its present form,[1] it consists of giving 100 mg dexamethasone dissolved in 500 ml of 5% glucose as a slow intravenous drip over 2 hours repeated on 3 consecutive days. On the second day, the patient is also given 500 mg cyclophosphamide in the same drip. This constitutes one DCP. Such DCPs are repeated at exactly 28 day intervals counted from the first day of the pulse. In between the DCPs the patient receives only 50 mg cyclophosphamide orally per day. The DCP regimen is administered in four phases. During the first few months (phase I) the patient may continue to develop recurrences of clinical lesions in between the DCPs and can therefore be given additional treatment (conventional daily doses of oral

corticosteroids or additional dexamethasone pulses) to achieve quicker clinical recovery, and these are as a rule withdrawn step-wise during the subsequent DCPs. After the skin and the mucous membrane lesions have subsided completely and the additional medication has been withdrawn, the patient is considered to have entered phase II. During this phase, the patient remains completely alright clinically but receives 9 more DCPs at exactly 28 day cycles along with 50 mg cyclophosphamide orally per day. During the next phase (phase III), the DCPs are stopped and the patient receives only 50 mg cyclophosphamide orally per day for the next 9 months. After this, the treatment for pemphigus is withdrawn completely and the patient is followed up for the next 10 years to look for a relapse if any (phase IV).

During the earlier part of our project, we used to give 6 DCPs during phase II and the duration of phase III was 12 months.

INDICATIONS AND CONTRAINDICATIONS

Since the pulse therapy regimen virtually cures every pemphigus patient for the rest of his life and there are almost no side effects, all pemphigus patients deserve to be treated with this regimen irrespective of whether they are having severe or mild disease. Even those patients who are in clinical remission but have to take maintenance doses of corticosteroids/ immunosuppressive drugs, can be made to give up the maintenance doses by administering them a course of the DCP regimen.

There are almost no contraindications. DCP therapy can be given to patients of all ages but the doses have to be reduced to half for children below the age of 12 years. It can also be given to patients having diabetes mellitus, hypertension, hyperacidity, osteoporosis, tuberculosis, etc., but each patient must receive additional appropriate treatment for the concomitant disease whenever necessary. Diabetic patients need to be given 10 units of soluble insulin for every 500 ml bottle of 5% glucose dissolved in the same drip in addition to the routine treatment for diabetes. Hypertensive patients must monitor the blood pressure regularly and adjust the treatment for hypertension if necessary. Patients having hyperacidity can continue to take antacids or H2 blockers as required and even those having active tuberculosis can continue the pulse therapy along with the anti-tubercular treatment. Viral warts and molluscum contagiosum can also be treated concomitantly along with the pulse therapy.

If a patient has severely infected lesions or there is a serious infection elsewhere, the start of the pulse therapy can be delayed for a week or two till the infection has been brought under control. Similarly patients having herpes zoster, herpes simplex or even chicken pox can be given concomitant treatment with acyclovir and the pulse therapy can be continued except under exceptional circumstances when the viral infection is very severe.

The only contraindication for pulse therapy is pregnancy or if the patient is a lactating mother and feeding her infant. This is also not an absolute contra-indication; the pulse therapy is only to be postponed till the patient has delivered her baby and stopped feeding the child. Till that time, the patient is to be maintained on a regular dose of corticosteroid just sufficient to keep the disease under control or even given a shot or two of dexamethasone alone in consultation with the obstetrician.

Patients who are unmarried or those who have not yet completed their family and want to have more children, have to be given only dexamethasone pulses (DPs) and not DCPs. Cyclophosphamide in the pulses has to be avoided because it can lead to amenorrhea or azoospermia in a significant proportion of patients. The low dose daily cyclophosphamide can be continued.

THE AIIMS EXPERIENCE

During the first few years, pulse therapy was given to only a few selected patients, especially those with severe disease.[9] However, the dosage schedule was haphazard and arbitrary as we were not sure of the total regimen. The patients were also irregular in follow up; they reported for the pulses at their own convenience and tended to stop the treatment by themselves. After about 2 years, a review revealed that several of the patients treated with the pulse therapy

had not developed any relapse for long periods without any maintenance treatment, and thus we realized that pemphigus could possibly be cured.[12]

Subsequently, we formulated an arbitrary regimen divided into 4 phases which was used to treat almost all pemphigus patients.[13-17] Several patients still did not complete the course and/or received the pulses at irregular intervals.[1] The relapse rates during follow up (recurrence of the disease after having completely recovered from the disease) were 53.8% in the patients who had received incomplete treatment and 18.2% in the patients who had received their DCPs at irregular intervals. Subsequently, we tried two modifications of the regimen. In the first modification, we increased the number of the mandatory DCPs during phase II from 6 in the original regimen to 9, and correspondingly reduced the duration of phase III from 12 months to 9 months. The relapse rate in the group who received the pulses at irregular intervals was 18.7% compared to 8% in the group who received their pulses at exactly 28 day cycles. In the second modification, we used only cyclophosphamide for the pulses during phase II of the regimen. The relapse rate in this group was 23.5%.[1]

All patients who developed a relapse were given the second course of the DCP regimen ensuring better compliance of the regimen. There were only a few patients who were persistent defaulters and needed more than 2 courses. The relapses in all cases were mild and responded easily to the next course.

Between 1982 and 1998, 500 pemphigus patients (pemphigus vulgaris 444, pemphigus foliaceus 33, pemphigus erythematosus 18, and pemphigus vegetans 5), with an almost equal sex ratio (251 males, 249 females) were enrolled for the DCP regimen. There were 44 patients younger than 20 years, 246 patients aged 20-40 years, 190 patients aged 40-60 years and 20 patients older than 60 years. Of these, 97 patients could not complete the treatment, and 19 patients died due to a variety of causes which were mostly unrelated to the disease or its treatment, or causes that were preventable with better patient management. The remaining 384 patients recovered from the disease and are living without any disease and without any maintenance treatment. Most of them have already crossed the 5 year post-treatment follow up period.[1]

This experience led us to conclude that pemphigus can be controlled in almost every patient and if the patient strictly follows the DCP regimen, he can be cured for the rest of his life. The treatment administered during phase II and III is necessary for ultimate cure; during phase II the most effective treatment consists of 9 DCPs taken at exactly 28 day intervals, with a daily oral dose of cyclophosphamide, followed by 9 months of daily cyclophosphamide during phase III. Compromises of any kind lead to inferior results and increase the chances of a relapse.

It is also important to remember that although the DCP regimen cures pemphigus, this does not mean that the patient has been protected from developing other diseases. The patient is as prone to develop other cutaneous or mucosal diseases as any other normal individual. Therefore subsequent lesions such as dermatophytosis, scabies, pyoderma or even lichen planus or aphthous ulcers in the mouth should not cause apprehension in the patient or the dermatologist that pemphigus has recurred. Several patients continue to develop aphthous ulcers in the mouth even during pulse therapy and this has often led some dermatologists to consider the DCP regimen as a failure in a small percentage of the patients. One should be able to distinguish aphthous ulcers from pemphigus ulcers because aphthous ulcers are far more painful, have a necrotic circular centre and an inflamed red periphery, and most ulcers heal within a few days, whereas pemphigus ulcers are far more persistent.

CLINIC EXPERIENCE

During the earlier experience at AIIMS, although almost every pemphigus patient recovered from the disease, in some patients the duration of phase I was very long as oral ulcers would persist for several months-years. After my retirement from AIIMS therefore, the DCP regimen was modified as follows:

Treatment in all patients with active disease was started with betamethasone 2-3 mg/day orally, ketoconazole 200 mg/day orally and 500 mg ciprofloxacin or cefadroxil twice daily, in addition to the DCPs and the

daily dose of 50 mg cyclophosphamide. The patients were also encouraged to clean the oral cavity with regular brushing of the teeth, and ignore the pain, the bleeding or the risk of peeling the oral mucosa. They were also advised to massage a topical corticosteroid gel on the oral ulcers 3-4 times a day especially after every meal.

This change in the regimen generally led to healing of all the skin lesions within 1-2 months and the oral lesions within 2-3 months. The antibiotic was withdrawn after all the skin lesions had healed and ketoconazole was withdrawn after the oral ulcers had healed, while the dose of betamethasone was reduced step-wise by 1 mg at the time of each subsequent DCP.

With this modification, the duration of phase I in almost all the patients was reduced to around 3-6 months, with the result that all the 20 patients enrolled during the year 1998 have already completed the treatment and are now in phase IV. Patients enrolled during the subsequent years are also following the same pattern.

SIDE EFFECTS

During the initial stages of the project, we had to evaluate the side effects of the large doses of corticosteroids and immunosuppressive drugs used. As a routine, we would admit every patient enrolled for pulse therapy and undertake a complete clinical and laboratory evaluation before starting the pulse and again after completing the pulse to look for side effects. Special care was taken to monitor the effects of the pulse on the total leukocyte counts, electrolyte levels, blood sugar levels (in normal individuals as well as in diabetic patients) and blood pressure values (in normotensive as well as hypertensive patients). The changes in all these parameters were found to be infrequent, insignificant and random, and possibly not related to the pulse administration. The admission period of the patients was therefore reduced to 3 days from the initial 5 days and the laboratory monitoring of the patient was restricted to the prepulse evaluation only.

Monitoring of the toxicity/safety on a long-term basis revealed that pulse therapy is extremely safe, it does not lead to an increase in the body weight unless the patient was receiving daily corticosteroids, and if the patient had already developed cushingoid obesity due to previous treatment the body weight and appearance would actually return to normal during the pulse therapy. There was also almost no risk of developing diabetes, hypertension, peptic ulceration, osteoporosis, striae, acne, hirsutism or other side effects commonly associated with corticosteroids unless the patient was receiving or had received conventional daily doses of corticosteroids. The risk of increased pyogenic infections on the skin, and candidiasis in the mouth persisted only as long as the patient had ulcers on the skin and oral cavity, and therefore vigorous treatment with systemic antibiotics and antifungal agents during this period was very helpful. Subsequently there was almost no risk. Similarly, viral or dermatophyte infections also needed to be treated on their own merit without interrupting the pulse therapy regimen. A few patients did develop reactivation of tuberculosis for which anti-tubercular treatment was given concomitantly without interrupting the schedule of the DCP therapy.

Similarly, side effects associated with cyclophosphamide were also generally very infrequent. Leukopenia, thrombocytopenia and anemia were rarely seen. Generalized hyperpigmentation was observed in 5 patients and hemorrhagic cystitis in another 5 patients, especially those who were irregular in their treatment and needed too many DCPs for effectively controlling the disease. Malignancy as a side effect of cyclophosphamide was not seen in any patient. The major side effects of cyclophosphamide in our patients were diffuse hair loss (which was reversible in all cases) and amenorrhea (and possibly azoospermia) in a significant proportion of patients. Subsequently therefore, for the patients who had not yet completed their family and wanted to have more children, we used only dexamethasone for the pulses (DPs), though the low dose daily cyclophosphamide was continued.[1]

The other side effects of DCP therapy included a feeling of weakness and tiredness due to corticosteroid withdrawal for 2-3 days after the pulse, bad taste in the mouth and loose motions coinciding with the pulses (both of which would respond to a 7 day course

of ciprofloxacin for 2-3 consecutive pulses), recurrent hiccup after the pulse (observed in a few patients), cataract (which was observed only in the elderly and could be coincidental), and bone pains and aseptic necrosis of the bones which were attributable more to the conventional daily dose treatment received earlier rather than the pulse therapy.

It was thus obvious that the pulse mode of administration was far safer than the daily dose regimens in spite of the high doses used, and considering its curative effect on the disease there is no justification for persisting with the conventional daily dose mode of treatment.

After having gained experience with the administration of pulse therapy, it also became clear that there was no need to hospitalize the patient (and no need to have continuous cardiac monitoring during the pulse, as practiced in the West). Slow administration of the dose over approximately 2 hours given in the same manner as any glucose drip in a day-care unit (at the AIIMS) or in a private clinic (post-retirement) is all that is necessary. The patients are, as a rule, sent back home after receiving the pulse. Patients having renal, hepatic or cardiac disease (especially arrhythmias) would certainly require clearance and appropriate treatment from the respective specialists.

IMMUNOFLUORESCENCE TESTS

Two types of immunofluorescence tests were undertaken in our patients: direct immunofluorescence (DIF) on the perilesional/normal-looking skin (to look for autoantibodies deposited at the intercellular areas), and indirect immunofluorescence (IIF) on the blood (to look for circulating intercellular autoantibodies). These tests were positive in almost all patients and helped confirm the diagnosis and monitor the response to the treatment, but occasionally they were negative even when the clinical diagnosis was undisputed and the titer of the autoantibodies was higher after treatment even when the patient had clinically recovered completely. We have encountered patients who continued to show positive DIF and/or IIF even 5 years after treatment without their disease relapsing. Thus, in our opinion the amount of treatment to be given should depend upon the clinical state and not the DIF/IIF results.

OTHER REGIMENS AND DRUGS

The selection of drugs and their dosages was completely arbitrary and based upon intuition and convenience. Whereas people in the West had used methylprednisolone, we preferred to use dexamethasone which was nearly 200 times cheaper. The dose of dexamethasone was fixed at 100 mg because it was easily available commercially. Three doses per pulse were considered to be adequate and convenient and found to be effective. The dose of cyclophosphamide for the pulse was also fixed at 500 mg for the sake of convenience and effectiveness without producing any serious side effects. It was however given only on one day of the pulse and not repeated earlier than 4 weeks. More frequent administration or using higher doses per pulse can lead to more frequent side effects. The oral dose of 50 mg cyclophosphamide per day had also been found to be safe because it does not lead to leukopenia and does not need any monitoring. The interval between the two pulses was fixed at 4 weeks for the sake of convenience, but later on it was realized that patients who did not follow the 28 day cycle had an increased risk of developing a relapse during the follow up, and it is necessary to administer the next pulse before the cells responsible for autoimmunity start proliferating again.

The most important decision made by us to achieve ultimate cure in pemphigus was to administer a standard dose of the treatment after clinical remission (the treatment given during phase II and phase III). If the treatment is stopped after completing phase I, almost every patient is expected to develop a relapse.

On learning about the success of our regimen, several dermatologists in other towns/institutions and even other countries have used the pulse therapy approach for treating pemphigus and other autoimmune diseases and many workers have introduced their own modifications. Some people have used methylprednisolone instead of dexamethasone, others have used larger or smaller doses of the corticosteroid, some have not bothered about the 28 day cycle for

repeating the pulses and some have used the oral route for administering the corticosteroid. Similarly, some workers have used only cyclophosphamide for the pulses while others have used azathioprine instead of cyclophosphamide. Basically, we believe that any combination of a corticosteroid and an immunosuppressive drug in comparable doses should produce similar results. Comparative studies may be undertaken but they are really not necessary. The combination of dexamethasone and cyclophosphamide is the cheapest and the safest. Methotrexate, azathioprine and cyclosporine are potentially more hazardous than cyclophosphamide. Similarly, placebo-controlled trials are also not necessary because each patient has acted as his own control whenever he has received treatment from other sources before starting the pulse therapy regimen, and the differences in the results are too obvious. Most patients treated with conventional regimens have died, while almost all the patients treated with the DCP regimen are alive (or have died due to unrelated causes).

Recently some workers have also used mycophenolate mofetil or intravenous immunoglobulin (IVIg) for pemphigus. These drugs/regimens have no doubt been successful in inducing remissions in pemphigus, but there is a tremendous difference between a remission and a cure/prolonged remission without maintainence treatment.

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