Dexamethasone pulse therapy in dermatology

The first report of the use of dexamethasone pulse therapy for a dermatological disease appeared in the pages of this journal two decades ago.[1] At that time, it represented a radical change in the approach to skin diseases as pulse therapy had previously been used mainly to prevent transplant rejection and in the treatment of lupus nephritis.[2,3] The therapy has since been used to treat a very large number of patients at several centers in India[4-11] and elsewhere.[12-17] This issue of the journal carries three articles describing the use of pulse therapy and its variants.

Details of the treatment regimens have been published previously.[4,18] Briefly, dexamethasone pulse therapy consists of the intravenous administration of 100 mg dexamethasone dissolved in 500 ml of 5% dextrose on 3 consecutive days. The pulses are repeated every 4 weeks. Cyclophosphamide 500 mg is given as an intravenous bolus on one day as part of dexamethasone-cyclophosphamide pulses (DCP) in pemphigus and other diseases; these patients also receive 50 mg cyclophosphamide daily orally between the pulses. In some patients, to achieve a quicker remission, daily oral corticosteroids and/or 2-weekly boluses of dexamethasone are used in addition. In pemphigus, phase II of the regimen begins when complete clinical remission has been achieved. During this phase, the patient receives 9 more DCPs along with 50 mg cyclophosphamide orally per day. In phase III, the pulses are discontinued and the patient receives only oral cyclophosphamide 50 mg a day for another 9 months.

Several factors have contributed to the success and widespread acceptance of dexamethasone pulse therapy. One important factor was the choice of corticosteroid. Conventionally, methylprednisolone was the agent most commonly used in corticosteroid pulse therapy. The choice of dexamethasone made the treatment considerably more affordable and accessible to patients. There was concern among some workers about the equivalence of 1000 mg of methylprednisolone and 100 mg of dexamethasone and some groups have administered pulses of 136 mg of dexamethasone.[5] However, a dose of 1000 mg of methylprednisolone is as arbitrary as a dose of 100 mg of dexamethasone, and in the absence of evidence that 136 mg pulses of dexamethasone are more effective, nearly all centers continue to use 100 mg boluses. There was initial alarm and anxiety about the large doses of corticosteroids and cyclophosphamide involved, and in the early days some centers would administer the therapy in the ICU under continuous cardiac monitoring. It is now given as a routine infusion, often in a day care or OPD setting, with the patient going home a few hours after completion of the infusion.

Another factor responsible for the effectiveness of pulse therapy is that the treatment has evolved in response to observations of the results of treatment in patients who were receiving this form of therapy.[19] Initially, only dexamethasone pulses were used. Cyclophosphamide boluses were added because relapses were frequent with dexamethasone alone. Earlier, patients received only monthly pulses of corticosteroids but with the observation that many patients developed some degree of recurrence of lesions between pulses in the early stages of therapy, daily oral corticosteroids were added in the first few months. Patients with extensive, active disease are also given interval pulses of dexamethasone during this phase. The current recommendation of administering 9 pulses after achieving clinical remission (phase II) and 9 months of oral cyclophosphamide therapy after stopping the pulses (phase III) was also arrived at by observing the relapse rate in patients who were treated with varying lengths of therapy. Similarly, the insistence on a strict 28-day cycle for pulses is based on the observation that relapses were commoner in those who took pulses irregularly.

Dexamethasone-cyclophosphamide pulse therapy is primarily used for pemphigus (and most of the preceding comments refer to this indication). It was initially described as a treatment that produced quick control of the disease and reduced hospital stay in pemphigus.[20] Later, it was noted to lead to long lasting remissions even after stopping therapy, virtually amounting to "cure".[21-26] Pulse therapy has also been used for other conditions, chiefly autoimmune diseases, and found to be an effective therapy. Several papers have reported its effectiveness in systemic sclerosis.[8-10,28] By extension, other conditions associated with increased dermal sclerosis and fibroblastic activity such as generalized morphea, keloids, post-burn contractures and scleredema have also been treated. The treatment is also effective in other autoimmune conditions like bullous lupus erythematosus,[30] dermatomyositis and pyoderma gangrenosum.[11,31,32] The enthusiasm for a new and effective treatment has led to its use in a small number of patients with a wide variety of difficult-to-treat conditions including multicentric reticulohistiocytosis,[32] prurigo nodularis,[33] disseminated porokeratosis,[34] urticarial vasculitis,[13] toxic epidermal necrolysis,[17] Stevens-Johnson syndrome,[15] generalized lichen planus, extensive alopecia areata, extensive, rapidly spreading vitiligo, sarcoidosis, Peyronie's disease, Darier's disease and Hailey-Hailey disease.[27] Larger studies are required to establish the role of dexamethasone pulse therapy in these disorders.

The adverse effects of pulse therapy are those of its constituent drugs, corticosteroids (infections, diabetes mellitus, hypertension, hyperacidity, and osteonecrosis) and cyclophosphamide (leukopenia, hematuria, gonadal failure, pigmentation, and hair loss).[19]These side effects are infrequent compared to daily corticosteroid therapy. Side effects peculiar to pulse therapy include hiccups,[35] facial flushing,[36] diarrhea, weakness, generalized swelling and weight gain, joint and muscle pains.[12] These side effects are usually observed with each pulse and last for a few days afterwards.[19] Most patients are able to tolerate these symptoms and continue treatment. On testing, pituitary-adrenal function was found to be suppressed in about half the patients 1 month after the last pulse of phase II. However, all these patients were asymptomatic and remained well during subsequent follow up and thus the clinical significance of the abnormal test results is unclear.[37]

Where do we go from here? We need to have reports from other centers that use pulse therapy to confirm that the guidelines formulated for DCP therapy are effective in producing remissions and preventing relapses. We need to identify problem situations that require modifications of pulse therapy and to rigorously examine that the modifications actually work. One such problem pointed out by the Hyderabad group is the patient in whom the disease smolders for many months. They comprise a small minority of patients who are seen in nearly all the large centers where pemphigus is treated. In spite of regular treatment, including daily corticosteroids and interval pulses, these patients do not have a remission of their clinical lesions for many months. These patients may benefit by a change in the adjuvant as was seen in two patients reported by the Hyderabad group who responded after they were switched to dexamethasone-methotrexate pulse. Another option may be the addition of another immunosuppressive agent to DCP therapy. This will require close and careful monitoring of the patient but may lead to a shorter duration of treatment and fewer side effects.

At the other extreme, we also need a way to identify those patients who respond to treatment and have long lasting remissions even though they have taken DCP therapy for a very short time. Attempts should be made to identify such patients early in the course of treatment so that they may be given a briefer or abbreviated course of therapy. This will reduce the burden of repeated visits to the hospital and prolonged therapy.

Another change in the DCP therapy that may be considered is the omission of daily doses of cyclophosphamide when pulse doses are being administered. Daily cyclophosphamide is not usually required when monthly boluses are administered, as in the treatment of lupus nephritis. It would be worthwhile to evaluate if the results of DCP therapy can be achieved without daily cyclophosphamide therapy while pulses are being given (i.e. during phase I and II). It may be given only in phase III. Other variations that have been practiced include oral pulses

with dexamethasone or betamethasone, administration of boluses of cyclophosphamide without boluses of dexamethasone, and the use of azathioprine or methotrexate with monthly pulses of dexamethasone.

All these variations need to be compared with the original DCP schedule both for the rapidity of control of disease and for the length of remission achieved after stopping the treatment. Every evaluation of pulse therapy, its variants or indeed any treatment for pemphigus should report three clinical outcomes: the time to clinical remission, the duration of remission while on treatment and the duration of remission after withdrawing treatment. This will enable valid comparisons to be made between different treatments.

Finally, though we know that DCP therapy works very well in practice, there is little information about the basic science aspects of this treatment regimen. Pharmacokinetic studies and studies of the effects of the therapy on the immune system may help us to understand the mechanism of action and refine this path breaking therapy further.

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