Pulse therapy for pemphigus: The burden of proof

Sir,

Recent retrospective case series on dexamethasone

cyclophosphamide pulse (DCP) therapy for pemphigus concludes with "the modifications employed in this study could ensure the cure of all pemphigus patients", "with DCP therapy…pemphigus can now be considered to be a completely curable disease", and that "pulse therapy should be the first (and the only) choice for treatment in all pemphigus patients until some better regimen evolves".[1] These conclusions are unacceptable for the following reasons.

Out of 143 patients selected, results are reported for 123. Patients' characteristics (e.g., age mean (SD), duration of disease, previous treatment, body surface area affected, severity, general condition, number of patients with oral, skin, and both involvements, concomitant diseases, etc), which help in deciding whether similar results may be obtained in other patients, are not mentioned. Seventeen patients did not start/continue the treatment, while three died during treatment. Statement about the 17 patients doesn't clarify reasons for drop-outs. Causes of deaths of three patients and whether autopsy was performed are not mentioned. These 20 patients are not included in analysis. This seriously overestimates the intervention effect, a situation akin to doing as-treated analysis instead of intent-to-treat analysis.[2] Apparently, patients received treatment as outpatients (no mention of admission). Despite pulse therapy being experimental (i.e. not based on randomized controlled trials' results as discussed below), patient consents were not taken.

All patients received same doses of medications irrespective of body weights. Patients with diabetes (number unknown) were given the pulses in 5% glucose (with insulin; normal saline would be better). Unmarried patients and those willing to have children were given 50 mg cyclophosphamide daily during phase I (about 3 months to >12 months), and phases II and III (9 months each) (i.e. about 21 months to >30 months; cumulative doses of approximately 31.5 g to >45 g). Cyclophosphamide produces cumulative dose-dependent gonadal failure.[3] Standard recommendation forbids use of cyclophosphamide as a first-line drug for men and women wishing to conceive post-treatment.[3] Cyclophosphamide is also teratogenic, but pregnancy tests were not done in female patients and contraception advice is not mentioned.

Only general statements are written about adverse events. Their frequency, severity, times of occurrence, actions taken, and further management are not mentioned. Although dual energy X-ray absorptiometry was not done, it is mentioned that osteoporosis does not occur with pulse therapy. Adverse events are attributed to daily oral betamethasone given in phase I, the doses of which were miniscule to probably produce significant effects. Pulse therapy can result in all usual glucocorticoid complications, as well as cardiac arrhythmias and sudden death.[4] A study from India has also reported several other adverse events due to DCP therapy.[5]

Patients were investigated pretreatment and after phases II and III of nine months each. Average duration of phase I is not written, but it lasted from about 3 months (in 62 of 123 i.e. 50% patients and not in 'most of the cases' as written) to >12 months. Thus, the investigations to examine toxicity of cyclophosphamide and high glucocorticoid doses for taking corrective actions were performed not according to standard guidelines,[3,6] but after enormous intervals. Brand names of medicines used are not mentioned (a standard practice in international journals), yet relapses in some patients are attributed to spurious medicines. It is written that pulses be given exactly at 28-day intervals and phases II and III be of nine months each, yet no reasons (e.g., comparison with other studies) regarding strict desirability of these durations are provided.

Fatal arrhythmias, myocardial ischemia and cardiac arrest, severe bradycardia, atrial fibrillation, ventricular arrhythmias, potentially life-threatening hyperkalemia, and increase in blood pressure and blood glucose may occur during, and in the days after, high dose 'pulse' glucocorticoid treatment.[7-9] Some cardiac effects are usually delayed and appear several hours after last infusion and last for several days,[8] necessitating close clinical, blood pressure and electrocardiographic monitoring.[7] As patients were treated on outpatient basis and it is not mentioned for how long after pulse administration they were observed or whether and for how long electrocardiographic monitoring was done, possibility of serious adverse events after their leaving clinic exists. Examining causes of death in the three patients was important. Furthermore, all patients who had skin lesions were given antibiotics, although frequency of bacterial skin infection is unknown. Patients received ciprofloxacin or cefadroxil (number of patients receiving either unknown). Cephalosporins can induce or aggravate pemphigus.[10] These patients

received antibiotics till skin lesions healed (several months). It is safer to use antibiotics other than cephalosporins and to use any antibiotic only to treat existing infection to prevent resistant organisms.

Dr. Pasricha's influence in India with regard to treatment of pemphigus is noticeable. Despite our admiration of him, examining the evidence backing above-mentioned claims is important. Astronomer and rationalist Carl Sagan once said that extraordinary claims require extraordinary evidence.[11] Science is self-questioning; experiments test our hypotheses. For knowing treatment effect, these experiments are randomized controlled trials (RCTs). In the hierarchy of evidence, expert opinion is at the lowest level and next is case series, lagging considerably behind conclusive evidence.[12] RCTs (and meta-analysis) are the gold standards for determining treatment efficacy. Probably due to precisely these reasons (i.e. lack of evidence of efficacy) authors rightly forbade ayurvedic and homeopathic medicines.

Searching evidence, we found no RCT that tested efficacy of DCP therapy. Closest to evaluating this therapy was an RCT[13] in which 11 patients received intravenous 100 mg dexamethasone on three consecutive days with cyclophosphamide (500 mg) on day one (D/C group). Pulses were initially repeated every 2–4 weeks and then at increasing intervals. In between pulses, oral cyclophosphamide (50 mg) was given daily for six months. The control group (11 patients) received oral daily methylprednisolone (2 mg/kg) and azathioprine (2–2.5 mg/kg), subsequently tapered (M/A group). Two years after treatment initiation, 5/11 patients in D/C group were in remission and 6/11 patients had progression. In M/A group, 9/11 patients were in remission and one had progression. There were more relapses with M/A therapy after remission; also side effects were more common. These differences were insignificant. Authors concluded that because of high number of progressions with D/C therapy, they could not confirm the encouraging results of earlier reports.

Until RCTs clearly show superior efficacy of DCP therapy in pemphigus, patients' best interests will be served by treatment comprising daily oral prednisolone and a glucocorticoid-sparing drug. Efficacy of prednisolone is enhanced with a cytotoxic drug.[14] In this RCT, the most efficacious cytotoxic drug for glucocorticoid-sparing was azathioprine versus cyclophosphamide pulse (1000 mg monthly) and mycophenolate mofetil. Without evidence, it is premature and unscientific to favor pulse therapy for pemphigus. Let science be a candle in the dark.

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