Pulse therapy - Credibility of evidence

Sir,

We read with great interest the letter by Singh and Chaudhary[1] in response to the article by Pasricha and Poonam entitled 'Current regimen of pulse therapy for pemphigus: Minor modifications, improved results'.[2] They meticulously discussed the drawbacks of the study in question and at the end almost dismissed pulse therapy as a treatment option for pemphigus. They have cited the reference of Rose *et al*.[3] while trying to prove the worthlessness of pulse therapy in pemphigus.

We agree with their views that there are drawbacks in the present protocol proposed by Pasricha and Poonam in treatment of pemphigus. But these are only minor. By judicious use of intervening betamethasone and systemic antibiotics for short periods, these can be taken care of. The concerns about long-term antibiotics and cyclophosphamide in those who wanted to have children have rightly been pointed out and discussed by Ramam in the same issue.[4] By and large, our views on pulse therapy in pemphigus are similar to those of Pasricha and Poonam. Corticosteroids still remain the treatment of choice for treatment of pemphigus. Side-effects associated with long term use of corticosteroids had stimulated the search for steroid sparing adjuvants effective in pemphigus. MEDLINE search with keywords 'corticosteroids in pemphigus, randomized controlled trial' (accessed 31st March 2009) yielded only 12 studies, of which only 10 were relevant, the latest being that by Werth *et al*.[5] However, Werth *et al.* in their article published in January 2008 in Archives of Dermatology mention that there are only two randomized controlled trials before their study assessing the efficacy of treatment regimens in management of pemphigus. Therefore, randomized controlled trials (RCT), considered the highest level of evidence in scientific literature are rare for management strategy of pemphigus. We must not forget that pemphigus is a rare disease in West and adequate number of patients for RCT may not be available.

Singh and Chaudhary referred to the trial by Rose *et al*.[3] which is indeed a randomized clinical trial. However, the dexamethasone cyclophsphamide treatment protocol (D/C) was significantly different from that originally preached by Pasricha *et al*.[6] Pulses were repeated every two to three weeks initially and then increased gradually to an interval of four, five and six weeks depending upon the response. If no relapse occurred at pulses at six-week intervals, cyclophosphamide pulse was stopped and dexamethasone pulse was continued every 12 weeks and then stopped. How long the dexamethasone is continued is not apparent from the article. After six months of treatment, oral cyclophosphamide is stopped irrespective of response to treatment, fearing long- term side effects.

In the methylprednisolone (MP)-azathioprine group (M/A), patients received 2mg/kg/day methylprednisolone and 2-2.5 mg/kg/day of azathioprine. If there was progression of the disease, MP dose was increased to 3 mg/kg/day. After cessation of new blister formation, MP dose was gradually tapered off and then azathioprine. The basic difference in these two regimens were that in the D/C group, the steroid sparing agent was discontinued after six months of treatment irrespective of disease status while in the M/A group, the MP dose was increased conveniently if there was no response and the steroid sparing agent was tapered off after that. We feel that D/C group might have not been given a level playing field for comparison to the other group.

There is another contradiction in the said study. They have mentioned that if a patient in D/C group was found to have progression of disease after six months of treatment, he was shifted to some other treatment while they have assessed the status of the disease at 24 months of study when it was found that 6/11 patients in D/C group had progression. What happened to these patients between six months and 24 months is not clear.

As far as side-effects are concerned, 15 incidences of side-effects were observed in the D/C group while there were 31 incidences in the M/A group, though the authors mention that they were comparable with $p>0.05$! Treatment had to be discontinued in one patient in the M/A group due to severity of side effect.

It is true that RCT provides highest level of clinical evidence, but it should be properly designed. It is desirable if we do not disregard a particular treatment regimen based upon a RCT, which uses different treatment protocol and results are confusing.

The original dexamethasone-cyclophosphamide pulse (DCP) regimen pioneered by Pasricha *et al.* is indigenous and has been used in different centers in India since mid 80s with excellent results. Our experience[7,8] (though we did not perform any RCT, as we do not feel the need for same) is that properly executed and monitored DCP therapy is reasonably safe and effective in treatment of pemphigus and those patients who do not respond to conventional oral prednisolone and steroid sparing agent or those who develop side effects can be effectively treated with DCP therapy. This in itself is a strong point in favor of efficacy of DCP in pemphigus vitiating the need for RCT. By all these studies, cure for pemphigus is shown. Finally, we advise Singh and Chaudhary to be cautious and polite in choice of their words while expressing their views on a scientific platform. Nobody in the present era can take the medical profession to ride just by personality and influence. Pasricha has indeed shown the world that pemphigus, a potentially fatal autoimmune blistering disorder can be cured with pulse therapy which he designed and for which he deserves all the credit.

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