Comparison of Two Steroid Regimens in Induction Therapy of Proliferative Lupus Nephritis: A Randomized Controlled Trial

Sir,

Oral prednisolone is usually started at doses ranging 0.5–1 mg/kg/day, with taper over the 6 months in the induction therapy of lupus nephritis (LN). Zeher *et al*.[1] reported low-dose steroid (0.5 mg/kg/day oral prednisolone) to be equally effective in inducing remission in proliferative LN flare compared to standard-dose steroid (1 mg/kg/day oral prednisolone) along with mycophenolate mofetil (MMF). All patients in the study by Zeher *et al*.[1] were on maintenance immunosuppressants before enrolment. We conducted an open-label, randomized, parallel group pilot study comparing low dose (0.5 mg/kg/day) with standard dose (1 mg/kg/day) of oral prednisolone as induction therapy of treatment-naïve proliferative LN patients at a single center. Patients between the ages of 12 and 70 years with a diagnosis of systemic lupus erythematosus (SLE) as per the American College of Rheumatology criteria[2] and biopsy-proven class III, IV, III+V, or IV+V LN based on the International Society of Nephrology/Renal Pathology Society classification[3] were included. Those with the presence of crescents ≥50% of the glomeruli, any prior use of steroids and immunosuppressive medications for any indication, serum creatinine >2 mg/dl, neurological or pulmonary lupus, and pregnancy were excluded. The study was approved by the Institute Ethics Committee and was registered with the Clinical Trial Registry-India (CTRI/2016/01/006488). Informed consent was obtained from all study participants, and the study fulfilled the ethical standards of the committees on human experimentation according to the Declaration of Helsinki Principles 1975, as revised in 2000. Patients received either 0.5 mg/kg/day (low dose) or 1.0 mg/kg/day (standard dose) of oral prednisolone according to randomization for a period of 8 weeks, followed by reduction of dose of steroids by 0.1 and 0.2 mg/kg/day every 4 weeks in low-dose and standard-dose groups, respectively, to a maintenance dose of 0.1 mg/kg/day in both groups. All patients received hydroxychloroquine (6 mg/kg/day) as well as renin–angiotensin system blockade. The primary outcome was "treatment response," defined as a decrease in 24-h urine protein by ≥50% (if baseline 24-h urine protein <3 g/day) and ≥50% reduction in proteinuria plus decrease in the 24-h urine protein to <3 g/day in patients with a baseline 24-h urine protein of ≥3 g/day, along with stabilization or improvement in serum creatinine (within 25% of the baseline). The secondary outcome were complete remission and partial remission defined as per the Kidney Disease Initiative Global Outcome criteria.[4] Of 45 patients screened, a total of 20 patients (fulfilling both inclusion and exclusion criteria) were randomized in a 1:1 ratio to 1-mg/kg/day steroids (n = 10) or 0.5-mg/kg/day (n = 10). All patients received methylprednisolone pulses of 750 mg/day for 3 days preceding oral steroids and MMF (titrated up to 2 g/day) as the adjuvant immunosuppressant. A sample size of 60 was planned on a pilot basis, and at the completion of one-third of the sample size, an interim report was performed which suggested strikingly inferior response in the low-dose steroid regimen, which led to the termination of the trial. The baseline characteristics of the patients did not differ between the two intervention groups [Table 1]. The mean (±SD) cumulative dose of prednisone at week 24 was 6345 mg in the standard-dose group and 3210 mg in the low-dose group (P < 0.001). Treatment response at week 24 occurred in 14 out of 20 (70%) of patients. At week 12 of therapy, 90% of the patients on standard-dose steroid achieved response compared to 20% on low-dose steroid (P = 0.002). Of 20 patients, 13 (65%) completed the 24-week study period according to planned interventions (per protocol). Six patients on low-dose steroid and one patient on standard-dose steroid were started on alternative induction therapy with a change in steroid dosing around week 16 for worsening proteinuria. All these seven patients were given tacrolimus (started at 2 mg twice a day, with target trough level: 4–8 ng/ml) in addition to MMF (500 mg twice a day) and steroids (0.5 mg/kg/day with gradual tapering after 4 weeks) as multitarget therapy. At week 24, all 10 (100%) patients on standard-dose steroid achieved response compared to only four (40%) patients on a low-dose steroid (P = 0.003), as per intention-to-treat analysis. Complete remission (CR) and partial remission (PR) was achieved in seven (70%) out of 10 and three (30%) patients on standard-dose steroid at the end of week 24, respectively. Only one (10%) patient on low-dose steroid achieved CR at week 24. The mean time to achieve response was 5.3 months in low-dose compared to 2.1 months in standard-dose steroid group (P < 0.001). The trend of renal parameters over the study period in the two treatment groups is shown in Figure 1. The mean change in 24-h urine protein (−2.96 (±0.69); P = 0.036) and serum albumin (1.17 (±0.23); P = 0.01) from the baseline to week 24 was significant in the standard-dose steroid group only; serum creatinine values did not change significantly in both the groups from the baseline to week 24. Three patients on standard-dose steroid developed infections during therapy and none of the patients on low-dose steroid had infections. Two patients developed herpes zoster infection after 2 months

Table 1: Baseline demographic and clinical characteristics (mean±SD)

Parameter	Low-dose steroid (*n*=10)	Standard-dose steroid (*n*=10)	*P*
Age (years)	28.30±9.8	27.4±9.5	0.873
Weight (kg)	49.6±10.1	51.6±14.0	0.719
Height (cm)	150±6.8	153.6±4.4	0.187
Body surface area (m^2)	1.42±0.2	1.47±0.20	0.641
Mycophenolate mofetil dose (g/day)	2.00	1.9±0.21	0.168
SELENA-SLEDAI[#] score	13.9±5.10	16.4±7.67	0.402
Anti-dsDNA* (IU/ml)	260.8±158.04	272.4±147.01	0.867
C3 (mg/dl)	48.53±35.01	55.32±37.68	0.681
C4 (mg/dl)	8.51±5.38	10.85±8.42	0.468
Serum creatinine (mg/dl)	1.02±0.48	0.91±0.38	0.582
Serum albumin (g/dl)	2.55±0.83	2.65±0.89	0.804
Hematuria	20%	30%	0.606
Leucocyturia	20%	50%	0.160
24-h urine protein (g)	2.88±2.08	3.47±2.37	0.562
Hemoglobin (g/dl)	10.02±0.96	9.15±1.99	0.229
Total leucocyte count ($\times 10^3$/ml)	6560.0±2565.7	6612.0±2401.04	0.963
Platelet count ($\times 10^6$/ml)	2.72±1.44	1.61±0.58	0.037
Lupus nephritis class	Class III (±V): 80% Class IV (±V): 20%	Class III (±V): 50% Class IV (±V): 50%	0.350
Activity index score	6.70±2.75	6.70±2.21	1.000
Chronicity index score	0.60±0.84	0.60±1.35	1.000

[#]SELENA-SLEDAI: Safety of Exogenous Estrogens in Lupus Erythematosus National Assessment modification-Systemic Lupus Erythematosus Disease Activity Index, *Anti-dsDNA: Anti-double stranded deoxyribonuclease nucleic acid

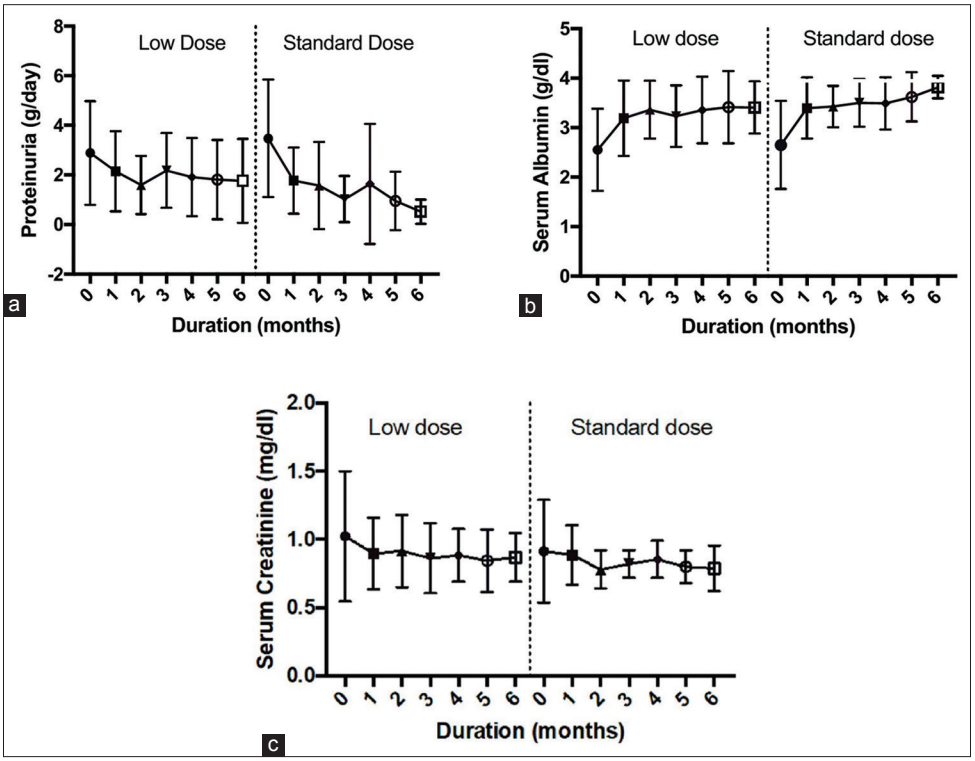

Figure 1: Mean change in renal function parameters from the baseline to week 24 in the two intervention groups. (a) proteinuria, (b) serum albumin, (c) serum creatinine

of treatment (managed successfully with oral antivirals) and 1 patient had cellulitis of the lower limb requiring hospitalization. Our findings suggest that oral prednisolone at 0.5 mg/kg/day is too low for treating proliferative LN in the induction phase and reflects the indispensable need of using high doses of steroids in treating LN.

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Conflicts of interest

There are no conflicts of interest.

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