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# Danazol in Treatment of Lupus Thrombocytopenia

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**SUMMARY** **Seven patients with systemic lupus erythematosus (SLE), persistent thrombocytopenia (TP), in whom it was considered undesirable to institute an increase in steroid or immunosuppressive agents, were treated with danazol. Five patients completed the minimum period of 8 weeks. Two patients showed early response to danazol but were switched over to cyclophosphamide or azathioprine after 4 weeks because of systemic disease. Of the remaining five patients, four had complete responses. In one patient who failed treatment the TP was considered to be related to another drug (ranitidine). Other manifestations of SLE also improved with treatment. Side effects included amenorrhea in one patient, and hypoglycemia and hyponatremia in another. Infections were absent. Danazol can be a useful alternative treatment of lupus TP:**

Danazol, a weak androgenic steroid, has been used in the treatment of sytemic lupus erythematosus (SLE)[1] because of its action on hormonal factors that have been incriminated in activity of SLE in both animal and human studies.[2-5] Danazol has also been used in treatment of idiopathic thrombocytopenic purpura (ITP)[6,7] and autoimmune hemolytic anemia.[8] The mechanism of action is uncertain and probably works through the T-cell immunoregulatory circuit.[9] Therefore, it is logical that danazol can be effective in patients with SLE and thrombocytopenic purpura (TP).[10] A study was conducted in our patients with SLE and TP, in whom it was undesirable to increase the dose of prednisone or immunosuppressive agents or who were refractory to the current regimen of immunosuppression.

## MATERIALS AND METHODS

All patients satisfied the ARA revised criteria for diagnosis of SLE.[11] In addition, the following criteria must be satisfied: 1) to avoid the possibility of spontaneous response or fluctuation of platelet count, TP must be present for at least 2 weeks before the commencement of danazol and was considered not to be due to the effect of immunosuppressive agents; 2) bone marrow aspirate and trephine biopsy were compatible with peripheral platelet consumption or destruction; 3) further increases in the dose of prednisone or immunosuppressive drugs were undesirable or the TP was refractory to the current therapy. Danazol 400 mg daily was given for 2 weeks and increased to 800 mg daily for a minimum of 6 weeks. Weekly hemoglobin, white blood cell and platelet counts were performed till the 8th week and then 4 weekly or as required. Routine clinical biochemistry, antinuclear antibody (ANA), anti DNA, C3, C4 and ESR analyses were performed. Anticardiolipin antibody (ACA) and lupus anticoagulant (LA) assays were performed as described.[12,13]

Complete response was defined by rise in platelet count to $\geqslant 100 \times 10^9/l$; partial response was defined as a rise to $50\text{-}99 \times 10^9/l$ and no response was recorded if the platelet count remained persistently $< 50 \times 10^9/l$. Student's $t$ test was used for statistical analysis where appropriate.

## RESULTS

Seven patients satisfied the in-

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clusion criteria over a period of three years and were recruited into this study. There were six females and one male. Their ages ranged from 18 to 38 years with a mean ± SD of 30 ± 7.9 years. The cumulative manifestations of SLE and the indications for use of danazol are shown in Table 1. Five patients were given danazol because of recent or past history of severe infection and one patient had refractory TP. The duration of TP before danazol therapy varied from 4 to 61 weeks with a mean ± SD of 22.3 ± 21.8 weeks. All of them were on steroids and one patient was on azathioprine at the time of commencement of danazol. Four patients (Nos. 3, 4, 5, 7) had evidence of subcutaneous bleeding.

Danazol was given for a mean duration of 38.6 weeks (SD ± 4.93 weeks). There was no concurrent change in steroid therapy during the weeks -4 to +4. Two patients (Nos. 1, 2) were switched over to cyclophosphamide or azathioprine after 4 weeks because of their systemic disease (Group I). Both Group I patients showed early response to danazol. The pretreatment platelet counts for these two patients were $44 \times 10^9$/l and $35 \times 10^9$/l, respectively. By week 2, the platelet count rose to $96 \times 10^9$/l and $109 \times 10^9$/l, and by week 4, to $202 \times 10^9$/l and $140 \times 10^9$/l, respectively.

Five patients (Nos. 3-7) completed the period of 8 or more weeks (Group II). Of these Group II patients, four had complete responses. Danazol was stopped in patient 7 who was also on ranitidine because the platelet count dropped to the pretreatment level after 20 weeks of danazol and there was a possibility of ranitidine-induced thrombocytopenia. The platelet count rose back to normal when ranitidine was stopped. Therefore, it was considered that the TP was likely to be related to randitidine and not due to SLE activity. Of the four responders, the platelet counts rose to $\geqslant 100 \times 10^9$/l in 6, 8, 12 and 28 weeks respectively (Table 2, Fig. 1). This observation suggested that it may take a considerable period of time (up to 28 weeks) for the TP to respond to danazol. This is un-

**Table 1.** Clinical Features of Patients on Danazol Therapy.

| Patient No. | Sex | Age at onset of SLE | SLE features* | Indication of danazol | Age at commencement of danazol | Duration of SLE before danazol (weeks) | Duration of TP before danazol (weeks) | Other SLE* manifestations at time of danazol | Steroid/immunosuppressive at time of danazol (mg/day) |
|---|---|---|---|---|---|---|---|---|---|
| 1 | F | 16 | K (II→IV), C,J.SZ, AIHA, TP | *Herpes simplex* | 18 | 30 | 4 | NS (IVc) | P40 |
| 2 | F | 35 | K,S.SZ, AIHA, TP | acute bronchitis | 38 | 37 | 10 | AP,S,LA,ACA | P15 |
| 3 | F | 29 | K (IV), C, J,S,AIHA, TP,LC | recent *Staphylococcus aureus* septicemia, no response after MP 550 mg | 38 | 112 | 12 | AIHA, LC, pleural effusion, anal ulcer | P30 |
| 4 | F | 21 | K (III→IV) C,J,AIHA, TP, LC | previous tuberculous meningitis | 26 | 62 | 8 | AIHA, LC,CRYO | P40 |
| 5 | F | 26 | K,C.J,TP, LC | leucopenia with AZA75 | 30 | 53 | 45 | AP,LC | P7.5 AZA50 |
| 6 | M | 25 | K (IV),C, J,TP,LC, AVN | leucopenia with AZA, previous *Nocardiosis*, avascular necrosis of both femoral heads | 35 | 127 | 61 | AVN both femoral head, LC | P10 |
| 7 | F | 15 | K (II→IVc) C,TP | No response with AZA | 22 | 82 | 16 | CRF | P15 |

* K = kidney involvement (WHO classification I–IV, C = crescentic glomerulonephritis, CRF = chronic renal failure); C = cutaneous; J = joints, S = serositis; SZ = seizure; NS = nephrotic syndrome; AIHA = autoimmune hemolytic anemia; TP = thrombocytopenia; LC = Leucopenia; AP = asymptomatic proteinuria; LA = lupus anticoagulant; CRYO = cryoglobulinemia; AVN = avascular necrosis; ACA = anticardiolipin antibody (IgG)
P = Predinisone/Prednisolone; AZA = azathioprine; MP = methylopredenisolone

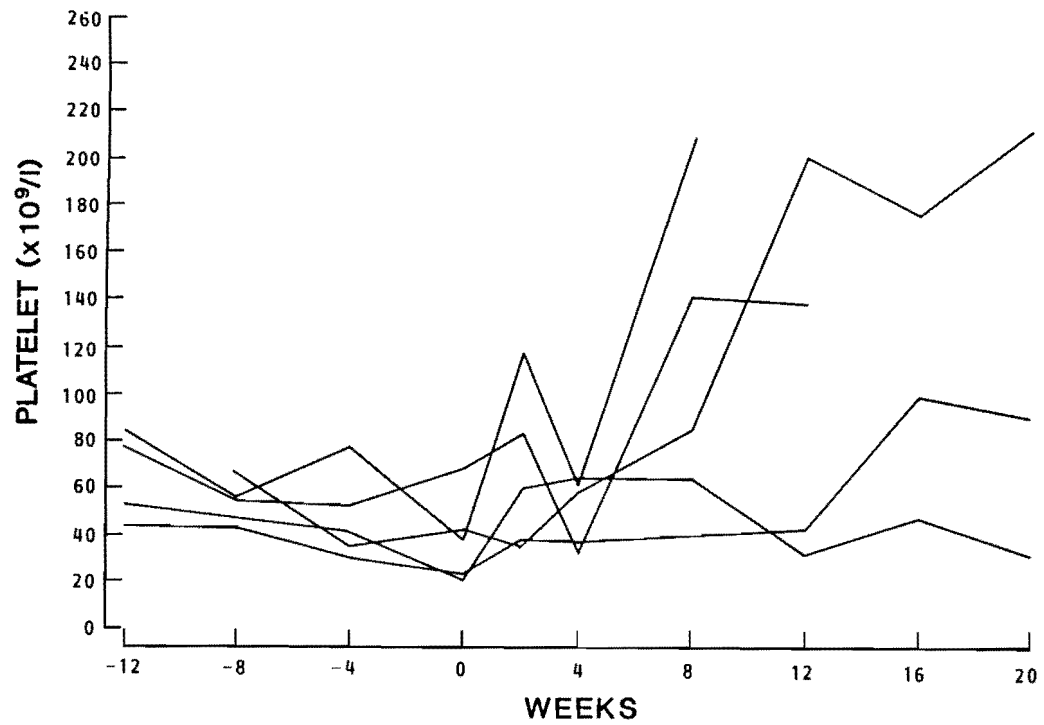


**Fig. 1** Platelet count after danazol therapy in patients treated for more than 8 weeks (n = 5).

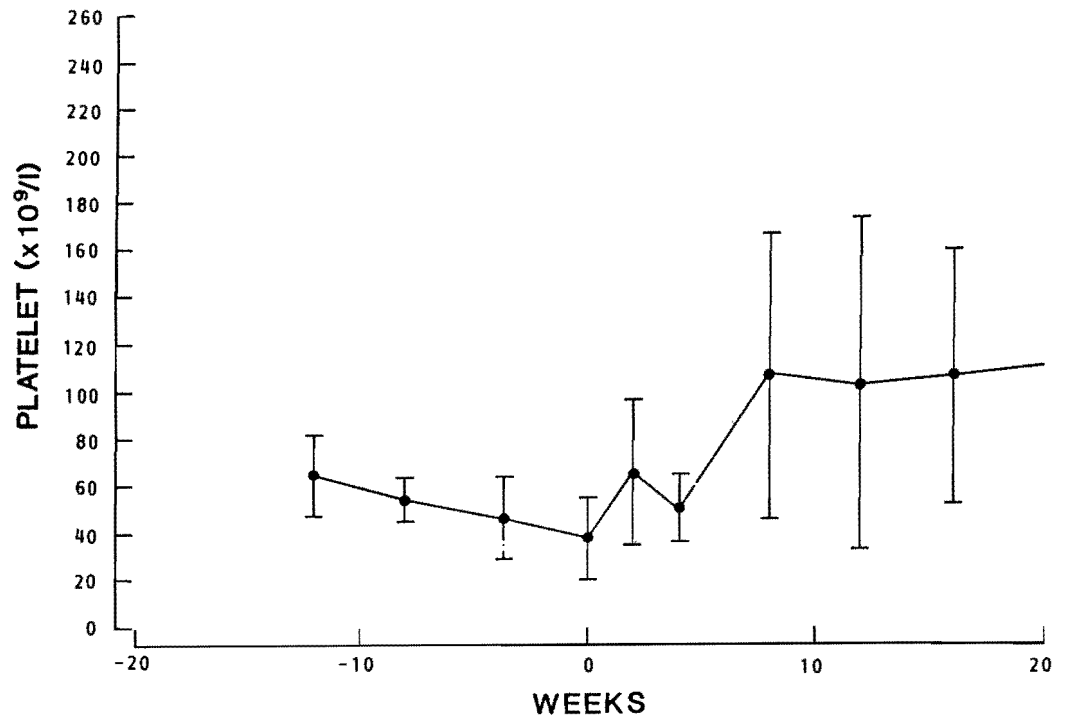


**Fig. 2** Overall platelet response to danazol therapy.

**Table 2.** Outcome of SLE Patients on Danazol Therapy

| Patient No | Lowest platelet before danzol ($\times 10^9$/l) | Duration from danazol to platelet $> 100 \times 10^9$/l (weeks) | Compli-cation | *Other improvement | Total duration of treatment with danazol (weeks) |
|---|---|---|---|---|---|
| 1 | 44 | 3 | nil | ↑ WBC | 4 |
| 2 | 18 | 2 | nil | NA | 4 |
| 3 | 38 | 6 | nil | healed ulcer, pleural effusion cleared up, ↑ Hb, ↑ WBC | 12 |
| 4 | 35 | 12 | nil | ↑ Hb, ↑ WBC CRYO | 104 |
| 5 | 33 | 8 | Ameno-rrhea | ↑ Hb, ↑ WBC | 16 |
| 6 | 20 | 28 | nil | ↑ WBC | 116 |
| 7 | 21 | – | nil | NA | 20 |

* NA = not applicable; Hb = Hemoglobin; WBC = white blood cell count; CRYO = cryoglobulin

likely to be due to spontaneous remission as the duration of TP before danazol was always longer than the time for the platelet count to rise above $100 \times 10^9$/l (Tables 1 and 2). The mean platelet count (± SD) before treatment, 2 weeks, 4 weeks and 8 weeks after tretment for Groups I and II patients were 38.4 (±18.9), 66.4 (±34.2), 50.6(±14.5), 107.6 (± 67.0) $\times 10^9$/l, respectively. When compared with week 0, the mean platelet count was higher at week 8 (week 2, $p = 0.096$; week 4, $p = 0.326$; week 8, $p = 0.01$; *t* test). ACA-IgG and LA were positive only in patient 2 (Table 1).

Two patients (Nos. 4, 6) received more than 100 weeks of danazol and platelet count remained persistently $> 100 \times 10^9$/l. Danazol was stopped afte 104 and 116 weeks, respectively and the platelet count remained $\geq 100 \times 10^9$/l 116 weeks and 62 weeks after stopping the therapy. The dose of prednisone was successfully tailed off in patient 6 and tailed down to 10 mg on alternate days in patient 4. In this latter patient, prednisone was given as a maintenance dose for her membranous lupus nephropathy.

**Improvement of other lupus manifestations**

Two patients with Coomb's positive hemolytic anemia responded to danazol (Nos. 3, 4). Of the five patients who completed ≥ 8 weeks of therapy, the hemoglobin rose from week 0 of 10.02 ± 2.51 (mean ± SD) to 10.8 ± 1.54 g/dl by week 8 (p = not significant). Five out of seven patient had leucopenia (LC) and white blood cell counts of these leucopenic patients were $> 4.0 \times 10^9$/l after danazol. One patient with serositis and vasculitic peri-anal ulcer and another patient with cryoglobulinemia resolved with the danazol therapy. ESR and ANA titer fell whereas C3 and C4 were increased during the danazol therapy but not reaching statistical significance (results not shown).

**Side effects of treatment** (Table 2).

During the course of first treatment, one patient (No. 5) developed amenorrhea, which was reversible after danazol was stopped. She was subsequently maintained on danazol 200 mg on alternate days without complications. Another patient (No. 3) had no complications from the first course of treatment. Danazol was taken off after 12 weeks. She was given a second course of danazol for recurrent LC and serositis. She developed hyponatremia (NA < 110 mmol/l and hypoglycemia (glucose 2.4 mmol/l). Danazol was stopped and she was given oral cyclophosphamide. The hypoglycemia and hyponatremia resolved 4 days after stopping the danazol.

## DISCUSSION

The predominance of female patients in SLE has been the center of argument concerning the etiopathogenesis of hormonal factors in SLE. Studies in animals and

humans have suggested that female sex hormones could be important.[2,3,14] Danazol, a weak androgenic steroid, could modulate the hormonal influence and effects on lupus activity.[1] In addition, Myalvaganam *et al*[8] reported a significant increase in the number of T cells and in the $CD4^+ : CD8^+$ ratio in ITP patients treated with danazol. This suggested that danazol can have additional immunomodulating actions.

TP is not an uncommon manifestation of patients with SLE. In our recent prevalence study on anticardiolipin antibodies in 91 patients with SLE, 59 patients (64.8%) had a history of TP over a mean follow up period of 91 months (SD 49.6 months, median 86 months).[15] Most of them responded to conventional therapy with prednisone or prednisone with immunosuppressive agents. These seven patients represented the only patients where danazol therapy was considered. The results in these seven patients were consistent with those of Marino *et al.*[10] Six of our seven patients with lupus TP responded to the therapy (Table 2) and some of the systemic complications also improved with danazol. The latter suggests that the action of danazol is not restricted to TP alone but probably affects the overall lupus process. In patient 5, the TP was refractory to prednisone and azathioprine and only normalized after danazol therapy. LA and ACA (IgG) were presented in one patient and did not change with danazol. It is difficult to conclude whether LA or ACA can be predictors of response. The previously reported side effects[10,16,17] of skin rash or TP was not seen in our patients. However, two major side effects were observed: amenorrhea and hyponatremia with hypoglycemia. Both were reversible after danazol was stopped. No infectious complication was identified. The latter characteristic is important for the use of danazol in patients with lupus TP. Steroids and immunosuppressives are the mainstays in treatment of lupus TP. However, in certain situations such as the presence of infection or important complications of these agents (e.g. severe leucopenia as in one of our patients), further use of such therapy may be hazardous. Danazol then becomes a good alternative. Further studies are underway to investigate the mechanism of action of danazol in the treatment of lupus TP.

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