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Hormonal manipulation of the immune response in systemic lupus erythematosus: a drug trial of an anabolic steroid, 19-nortestosterone

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SUMMARY Ten patients (8 female, 2 male) with systemic lupus erythematosus (SLE) were entered into an open trial with the anabolic steroid 19-nortestosterone (19-nor). Their clinical condition did not improve, nor were significant changes observed in the majority of laboratory data. However, overall the platelet count rose, and in patients with abnormal levels of T lymphocytes bearing receptors for IgG Fc treatment returned the values to normal. Despite this latter result, suppressor cell activity remained slightly below the normal range throughout the study period.

Women are afflicted more than men by many rheumatic diseases[1]. There are qualitative and quantitative differences between the female and male immunological systems, which may in part at least be determined by the sex hormones.[2 3] The NZB/NZW F1 hybrid mouse (B/W) develops an illness similar to that of human systemic lupus erythematosus (SLE) and has provided a model for investigating the disease. There is earlier mortality in the female mouse, although prepubertal castration of male mice increases their premature death rate.[4] Androgens administered early or late in life to prepubertally castrated mice are effective in suppressing disease activity.[5 6] The anabolic steroid 19-nortestosterone (nandrolone) and its decanoate ester have also produced significant amelioration of disease in the B/W mouse, indicating that the therapeutic phenomenon might be distinct from the androgenic properties of steroids.[7]

Since there was experimental evidence for the efficacy of nandrolone (Decadurabolin) in the mouse, an open trial of this agent was undertaken in patients with a variety of clinical manifestations of SLE.

Patients and methods

Ten patients (8F, 2M; mean age 51 years) with SLE who satisfied the American Rheumatism Association criteria[8] were studied after informed consent and ethical committee approval had been obtained (Table 1).

Patients were assessed every 3 to 4 weeks. At each visit they received an intramuscular injection of nandrolone decanoate in oil in a dosage of 150 mg for women and 200 mg for men.

Investigations included routine haematological and biochemical tests and studies of antinuclear factor and DNA binding. Serial complement levels and C-reactive protein were measured by radial immunodiffusion.[9] Lymphocytotoxic antibody activity was measured at 20°C by standard techniques.[10]

Monospecific suppressor cell function was assessed by the method of Miller and Schwartz. [11] Care was taken to obtain blood samples at the same time of day at each visit and the results were compared with those from 19 normal subjects (11F, 8m). T-cell subpopulations bearing receptors for the Fc portion of IgG (Tγ cells) and of IgM (Tμ cells) were enumerated by an adaption of the method of Lydard and Fanger.[12] Instead of rosetting the T-cells with sensitised ox red cells, we used an inert bead matrix (Immunobeads, Bio-Rad Laboratories) coated with either IgG or IgM as the rosetting medium.

Results

The mean duration of treatment was a little over 6 months with an average total dose of 800 mg of nandrolone decanoate.

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Table 1 *Clinical features and laboratory data of patients with SLE*

Patient	*Clinical features*	*Existing therapy*	*Commencement of trial*	
			ANF	*DNA binding*
1	Polyarthritis, photosensitivity, thrombocytopenia, leucopenia	NSAID	1/256	84
2	Polyarthritis, photosensitivity pleurisy, Sjögren's syndrome, hypothyroidism	Prednisolone 10 mg/day	1/1000	8·8
3	Pleurisy, leucopenia, polyarthritis, alopecia myopathy, mouth ulcers	Prednisolone 5 mg/day	1/1000	40
4	Polyarthritis, photosensitivity, Raynaud's disease, discoid severe alopecia, thrombocytopenia, leucopenia	Prednisolone 5 mg/day	1/256	50
5	Polyarthritis, leucopenia, thrombocytopenia, Raynaud's disease, pseudobulbar palsy, photosensitivity	Prednisolone 7 mg/day	1/64	12
6	Photosensitivity, polyarthritis, alopecia, discoid LE, Raynaud's disease	NSAID	1/1000	20·4
7	Polyarthritis, leucopenia, thrombocytopenia	NSAID	1/256	49
8	Alopecia, mouth ulcers, polyarthritis, photosensitivity	NSAID	1/256	30
9	Photosensitivity, alopecia, Sjögren's syndrome, pleurisy, Raynaud's disease	NSAID	1/64	14
10	Pericarditis, polyarthritis, skin rash, photosensitivity, Sjögrens syndrome	Prednisolone 10 mg/day	1/256	50

NSAID = nonsteroidal anti-inflammatory drug. DNA binding normal <30%.

CLINICAL FEATURES

Five of the 10 patients showed no clinical deterioration or improvement (patients 5, 7, 8, 9, and 10). Of those who were worse, 3 were female and displayed deterioration with myopathy, arthritis, and low C4 (patient 3); increased severity of pre-existing skin rash (patient 4); and exacerbation of a chronic chest infection (patient 2). The last patient was the only one to have a raised C-reactive protein which remained so during the period of observation prior to and after treatment with 19-nor. One male subject (patient 1) developed steroid acne, with positive skin immunofluorescence to IgG and complement. The other male (patient 6) developed subcutaneous nodules on the extensor aspects of the elbows and pretibial regions.

LABORATORY INDICES

The overall results for the routine laboratory data were examined by Student's paired *t* test. The only significant changes were a rise in platelets (those patients thrombocytopenic prior to 19-nor remained unchanged) and a small drop in C4 and factor B levels. Overall Clq binding immune complexes remained unchanged.

Four of the 10 patients had lymphocytotoxins in their sera. Of these, 3 had a significant rise in lymphocytotoxicity, confirmed by 2-way analysis of variance ($p<0·05$) (patients 2, 3, 10). Rise in lymphocytotoxicity in patient 3 paralleled an exacerbation of her disease.

Seven of the 10 patients had Tγ cell levels which were outside the normal range. Five of these were depressed, while 2 were elevated. One remained high, but the remainder returned to normal or stayed within the normal range after the first 3 months of treatment. Tμ cell levels remained largely unchanged throughout the period of observation (Table 2). Concanavalin-A-induced suppressor cell activity showed no significant change and remained constant, slightly below the levels found in healthy adults at 84 ± 19 (SD)%.

Discussion

Overall, patients in this open trial did not benefit from 19-nor. Indeed they may have worsened clinically, although it is difficult to be certain, as one observation period may not reflect the number and severity of exacerbations in another.

Other authors reported very low levels for Tγ cells (reputed to contain suppressor activity) in SLE[13] or in some cases both high and low levels[14]; so the link with SLE is not absolute. Tμ cells (thought to contain T helper activity) were largely unchanged and did not differ significantly from those of normal control subjects. The levels found in this study accord with those of other studies.[13]

The changes in Tγ cell population were not accompanied by any increase in the level of concanavalin-A-inducible suppressor activity which might be expected to be the route by which autoimmune reac-

Table 2 *Effects of 19-nortestosterone treatment on T lymphocytes bearing Fc receptors for IgG and IgM*

Patient	*Treatment stage: % T lymphocytes bearing receptors**		
	Before	*During*	*After*
4			
Tγ	15	15	17
Tμ	31	36	38
10			
Tγ	8	14	15
Tμ	29	30	37
3			
Tγ	17	16	15
Tμ	36	38	37
2			
Tγ	25	18	17
Tμ	42	43	46
7			
Tγ	10	19	16
Tμ	40	34	31
8			
Tγ	11	22	16
Tμ	44	38	38
6			
Tγ	27	18	17
Tμ	34	34	41
1			
Tγ	15	15	15
Tμ	42	33	40
5			
Tγ	12	15	15
Tμ	33	34	45
9			
Tγ	10	16	21
Tμ	30	35	39
Normal subjects			
Tγ 15 ± 2			
Tμ 42 ± 9			

*Results expressed as the mean of 2 determinations.
†Results expressed as the mean (± SD) from 11 females and 8 males.

tivity could be reduced. It would appear from our results that suppressor activity is not completely related to Tγ cell levels. The dramatic therapeutic effect seen in the B/W mouse with 19-nor was not repeated in man. But comparison of the dosage showed that the mice received, weight for weight, over an equivalent period 20 times the quantity of drug.

In conclusion, this trial has shown that by returning suppressor T cell levels to normal, 19-nor can modify the immune system in human beings. This suggests that the search should continue for other steroids which will specifically modify components of the immune system and at the same time relieve the symptoms of SLE.

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