LEVAMISOLE IN THE TREATMENT OF SYSTEMIC LUPUS ERYTHEMATOSUS — PRELIMINARY RESULTS

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INTRODUCTION

Evidence that T-cell function is defective in patients with active Systemic Lupus Erythematosus (SLE) has been accumulating in the last few years (Scheinberg and Cathcart, 1974; Rosenthal and Franklin, 1975; Michlmayr et al, 1976). The recent finding of a clear-cut T-cell deficiency preceding the auto-immune disease in New Zealand Black Mice has further strengthened this concept (Talal and Steinberg, 1974).

Levamisole (LMS), an antihelminthic drug which has been available in Singapore for about 10 years was recently shown by Renoux and Renoux (1971) to have marked immunostimulating properties. This drug stimulates both the T-cell and B-cell divisions of the lymphoid system but the effect on the T-cells is much more marked. This drug has been administered to patients with rheumatoid arthritis (Huskisson et al, 1976; Runge et al, 1977; Veys and Mielants, 1978) and SLE (Gordon and Keenan, 1975) with encouraging results. These authors also reported that LMS therapy restored the immunological parameters of T-cell function back to normal.

The above findings prompted us to undertake a pilot study of the drug in a selected group of patients who has responded poorly to conventional therapy or who had developed numerous side-effects which necessitated frequent hospitalization.

MATERIALS AND METHOD

17 patients with SLE as defined by the criteria of the American Rheumatism Association (Cohen et al, 1971) entered the study. 16 were females and one male and their present age ranged between 16 to 53 years. Duration of illness as defined from date of first diagnosis varied from 129 months to 10 months with a mean follow-up period of 45 months. All were considered to have active disease by the usual clinical and laboratory criteria and were receiving corticosteroids of varying dosages continuously since diagnosis. 10 of the patients had more than 5 ad-

admissions since diagnosis and most of them exhibited side effects of steroid therapy. Attempts at reduction of steroids invariably resulted in exacerbation of symptoms. Three of the patients received immunosuppressive therapy but none of them was on this when the study commenced. Relevant clinical data are detailed in Table 1.

Before the exhibition of LMS, the following laboratory parameters were done:- Haemoglobin, BSR, Urea, LE cells, serum albumin, anti-DNA (double-stranded) antibody, total complement, C_3 and C_4. LMS was given in fixed doses of 150 mgm a day for 3 days continously every fortnight. No attempts were made to modify the existing steroid regime for a minimum period of three months. This was then subsequently changed (either increased or decreased) depending on the patient's response. At the beginning, patients were seen every fortnightly and had their total white cell and platelets estimated at every visit. After three months, most of them were seen once a month. All the laboratory parameters were repeated at 3 monthly intervals. Period of LMS treatment varied from 6-16 months with a mean period of 10 months. The results of the study are presented in terms of laboratory and clinical changes following the initiation of LMS therapy. Side-effects of LMS therapy together with its influence of steroid dosage are also noted.

RESULTS

Laboratory Data

(a) Serological

LE cells — Of the 17 patients in the study, 8 had positive LE cells at the time of initiation of therapy. During the period of treatment, 6 of them reverted to negative. No patient negative for LE cells at time of initial assessment became positive at any time during the course of therapy.

Anti-DNA (double-stranded) antibody — 10 pa-

TABLE 1: Detailed Clinical Data of Patients

Patient No.	Sex	Age at First Diagnosis	Date of First Diagnosis	No. of Admissions	System Involvement	Comments
1.	F	25	Sept 1967	5	Rash, joint, ITP, Cardiac, CNS, Pleural effusion	Frequent relapses, infections, allergic to many anti-biotics.
2.	F	16	April 1972	9	Rash, joint, nephrotic syndrome	TB abdomen, poor response to steriods.
3.	F	22	Jan 1973	6	Renal, CNS, GIT	Poor response. recurrent infective episodes.
4.	F	28	March 1973	9	Rash, joint	Steriod myopathy. avascular necrosis of hip, poor response.
5.	F	13	Sept 1973	8	Rash, joint, vasculitis, nephrotic syndrome, interstitial lung disease	Poor response, marked Cushingnoid, hypertension, recurrent infections, cataract.
6.	F	32	Jan 1974	7	Rash, joint, generalized lymphadenopathy	Poor response, frequent relapses.
7.	F	30	Sept 1974	2	Rash, joint, vasculitis, renal	Hypertension, diabetes, steroid myopathy, repeated chest infection.
8.	F	25	March 1975	9	Rash, joint, generalized lymphadenopathy, vasculitis, GIT, transient heart block	Recurrent relapses. Requires Pred 30 mgm/day for control.
9.	F	27	June 1975	6	Rash, cardiac, GIT, CNS, pleural effusion	Poor response, collapse vertebrae, lung abscess, tinea corporis.
10.	F	16	July 1975	4	Rash, joint, CNS, vasculitis.	Cushingnoid, hypertension.
11.	F	29	Sept 1975	7	Rash, vasculitis, CNS, renal	Hypertension, avascular necrosis of hip.
12.	F	28	Sept 1975	7	Rash, joint, CNS	Frequent relapses, cataract, frequent infections.
13.	F	25	Dec 1975	2	Rash, alopecia	Persistent facial rash.
14.	F	28	June 1976	2	Generalized lymphadenopathy, rash, joint, haemolytic anaemia	Steroid myopathy, hypertension.
15.	F	27	March 1977	4	Rash, joint, carditis, CNS	Steroid diabetes, myopathy. cataract, hypertension.
16.	M	53	May 1977	3	Rash, generalized lymphadenopathy, renal	Hypertension, diabetes, steroid myopathy, PTB.
17.	F	30	Sept 1977	2	Skin, joint	Severe Cushingnoid, hypertension.

TABLE 2: Changes in DNA, Total complement, C_3 and C_4values with LMS therapy

Patient No.	ds DNA (N < 25 Units)		Total Complement (N 21 - 43)		C_3 (N 53 - 118)		C_4 (N 18 - 58)	
1.	60	50	29	25	82	76	37	25
2.	10	4	8	15	23	49	5	9
3.	85	25	6	28	20	69	8	21
4.	55	35	20	33	24	82	16	30
5.	19	0	0	41	27	124	14	14
6.	103	110	8	20	24	56	4	13
7.	50	27	35	34	90	99	23	25
8.	52	41	12	23	22	74	6	17
9.	103	14	12	34	21	87	12	33
10.	6	N.A.	38	34	80	62	23	18
11.	19	5	23	30	75	66	12	19
12.	156	17	9	32	20	67	10	20
13.	50	45	24	32	36	79	7	11
14.	N.A.	4	N.A.	31	N.A.	76	N.A.	32
15.	110	14	7	44	17	87	5	25
16.	21	15	37	33	82	67	13	16
17.	15	24	34	32	69	72	13	17

N = Normal values
N.A. = Not available
ds = Double stranded

First column of figures refer to values before LMS therapy.
Second column refers to latest observation.

tients (Nos. 1, 3, 4, 6, 7, 8, 9, 12, 13 and 15) had raised DNA antibody levels on entry into the study. During the period of study, all the levels fell and 4 of them (Nos. 3, 9, 12 and 15) were normalized.

Total Complement (TC) — 9 patients had decreased total complement levels on entry into the study. All of them rose during the period of study and 8 of them were normalized.

C_3 and C_4 — 10 patients had diminished levels of C_3 and 13 had diminished levels of C_4 at the beginning of the study. At the end of the study, all their levels rose. 9 patients had normal C_3 levels and 8 had normal C_4 levels.

The changes in anti-DNA antibody, total complement, C_3 and C_4 are detailed in Table 2.

(b) Non-serological

We use three common non-serological laboratory data for comparison. We find both haemoglobin and serum albumin excellent indicators of disease activity (Fries and Holman, 1975). As with most studies, changes in BSR were non-specific and unreliable and this will not be reported.

Individual changes in haemoglobin and serum albumin are shown in Figs 1 and 2. There was significant increase in Hb (more than 1 gm) in 10 patients. Before therapy, 7 patients had a Hb below 10 gms. At the end of the study period, only 2 patients had a Hb below 10 gms. The mean change for the whole group was from a pre-LMS level of 10.1 gm to 11.4 gm at current observation. Similarly, significant rise in serum albumin occurred in 11 patients increasing from a mean pre-LMS level of 2.7 gm% to 3.9 gm% at present. Before the institution of LMS therapy, 11 patients had an albumin level below 3 gms%. At the end of the observation period, only 1 patient had a serum level below 3 gm%. As we use LMS only in non uraemic patients, no changes occurred in the blood urea levels.

CLINICAL CRITERIA

There is inherent difficulty in assessing patient response clinically in a disease that is so protean in its manifestations and variable in its course. We have, therefore, broadly grouped clinical response under (a) disease activity completely suppressed after initiation of LMS therapy (b) disease improved and (c) disease unchanged. Taking all the variables into consideration, the overall patient assessment was a follows:- the disease was completely suppressed in 5 patients, improved in 10 patients and unchanged in 2. No deaths occurred during the period of study.

In addition, we were able to drop steroid dosage in 11 patients — see Fig 3. In one of the two patients in whom we raised the Prednisolone to 60 mgm a day, it was subsequently realized that the rash was in fact due to LMS itself. This was initially mistaken for a

relapse of SLE. The mean drop for the whole group was from a pre-LMS level of 28 mgm prednisolone a day to a present level of 18 mgm a day.

DISCUSSION

Systemic lupus erythematosus is the commonest diffuse connective tissue disease in Singapore (Tay and Khoo, 1970). In spite of recent improvements in mortality trends (Dubois et al, 1974), there is still considerable mortality and morbidity (Feng et al, 1973a). Most of the deaths occur in a group of patients whose disease respond poorly to steroids. Immunosuppressives like cyclophosphamide has been used as adjuvant therapy (Feng et al, 1973b) but this drug too suffer from a number of serious side effects (Miller et al, 1971; Fairley et al, 1972; Buchanan et al, 1975). Gordon et al (1977) in a further report of 16 SLE patients treated with LMS and steroids noted a singular lack of significant side-effects. There was considerable reduction of a variety of clinical and laboratory parameters of the disease together with significant steroid-sparing effect.

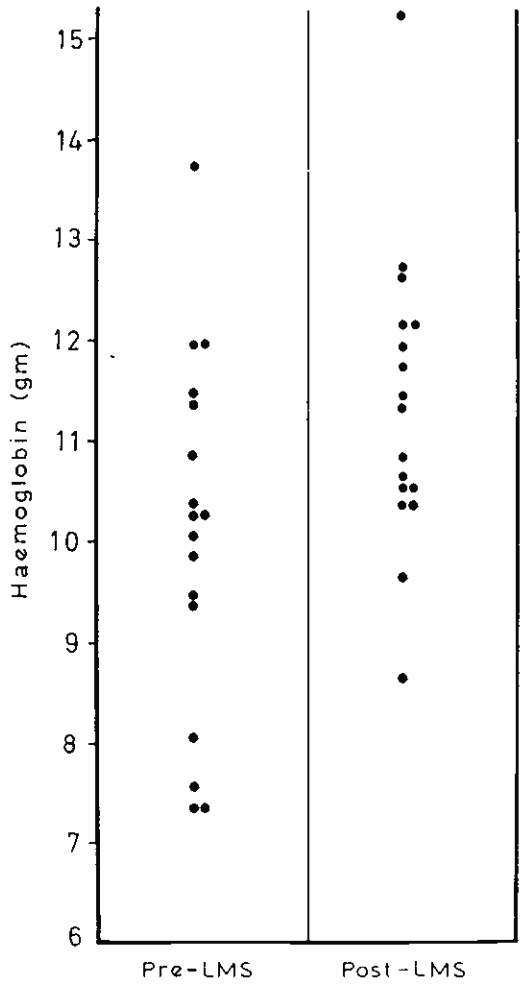

Fig 1 Individual changes in Haemoglobin with Levamisole (LMS) therapy

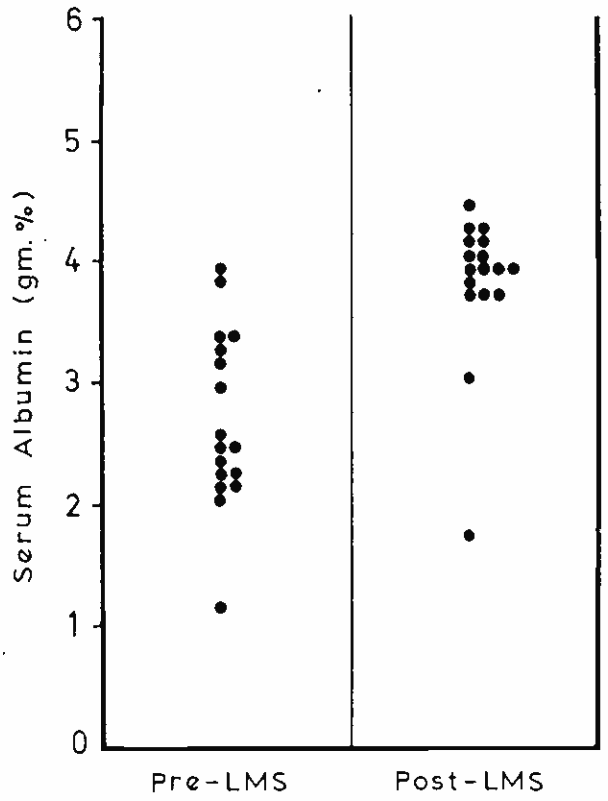

Fig 2 Individual changes in serum albumin with Levamisole (LMS) therapy

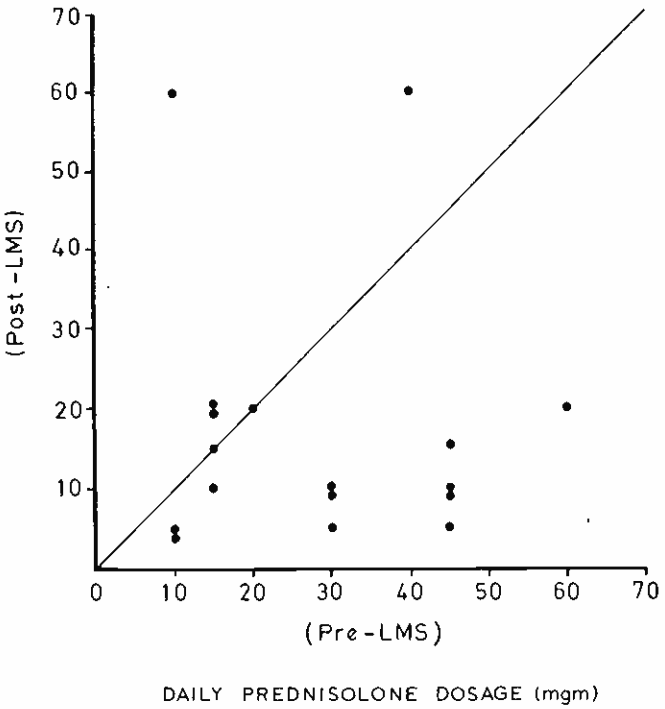

Fig 3 Changes in Prednisolone dosage with Levamisole (LMS) therapy

In this study, we noted improvement in 15 patients. The only significant side effect noted was skin rash and fever which necessitated discontinuance of the drug in three patients. One patient complained of a metallic taste. There was no occasion when we had to stop the drug because of leukopenia or thrombocytopenia although these and other side effects have been reported (Sigidin and Bunchuk, 1977; Schimidt and Mueller - Eckhardt, 1977; Macfarlane and Bacon, 1978).

Taking into consideration that majority of these patients responded poorly to steroids or were plagued by serious side-effects, we feel the present results are encouraging. Nevertheless, the basic question remains to be answered i.e. whether the addition of LMS to steroids has any synergistic effect or whether the improvements we have seen are in fact due to the continuing effect of steroids alone. There is experimental data to suggest that LMS may delay the reappearance of autoantibodies and decrease the histological evidence of lupus nephritis when given to New Zealand mice first treated with cyclophosphamide (Zulman et al, 1978). We believe this question can only be answered by a prospective randomized double blind study of new patients. Since it would be unethical not to used steroids in SLE patients, the design of the study should be such that all the patients receive steroids but one group in addition will receive LMS and the other group a placebo. Their response both in terms of clinical activity and laboratory status can then be assessed at regular intervals and compared. LMS in our experience and given under controlled conditions, is a relatively safe drug. Its current experimental and clinical status is well reviewed by Symoens and Rosenthal (1977).

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