PRELIMINARY DRUG STUDIES

FRENTIZOLE THERAPY OF ACTIVE SYSTEMIC LUPUS ERYTHEMATOSUS

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Frentizole is a benzimidazoleurea that has immunosuppressive properties in mice. Eleven steroid-treated patients with active systemic lupus erythematosus received frentizole (150–350 mg/day) in combination with stable or decreasing doses of prednisone in an open label trial. Nine patients completed at least one 21- to 75-day course of therapy with this drug. Clinical parameters of disease improved in 8 of these 9 patients. Mean DNA binding decreased by 28%, mean CH50 increased by 20%, and mean absolute lymphocyte and T cell counts decreased by 25–26%. Granulocytopenia was not observed. Three patients developed reversible hepatic toxicity. Clinical and serologic improvement was noted in 3 patients who accepted a second 90-day course of frentizole therapy.

Frentizole, a benzimidazoleurea [1-(6-methoxy-2-benzothiazolyl)-3-phenyl urea, Compound 53616, Eli Lilly Company], was developed to provide an alternative to cytotoxic antineoplastic agents which are used to treat selected autoimmune diseases (1). This drug was selected for testing in humans after initial screening showed that it had immunosuppressive properties in mice (2–4). In the NZB/NZW mouse model of systemic lupus erythematosus (SLE), therapy with frentizole prolonged life and decreased proteinuria (4,5). Frentizole had a therapeutic index 3 to 7 times greater than cytotoxic antineoplastic drugs and was synergistic with cortisone (4,5). When frentizole was given to mice in a dose greater than the amount needed to cause immunosuppression, the incidence of infection was not increased (6). In experimental animals, therapy with frentizole was associated with anemia, hepatic toxicity, and thyroid toxicity after large doses were given over an extended period of time (5,7). The effectiveness of this drug as an immunosuppressive agent and its relatively low toxicity in animals prompted us to design a trial to determine if frentizole had immunosuppressive and/or toxic effects in patients with SLE.

PATIENTS AND METHODS

Eleven adult SLE patients were enrolled in the trial (Table 1). Each patient met the five predetermined selection criteria outlined in Table 2. Patients with one or more of the following findings were excluded: central nervous system lupus; lupus pneumonitis; infection; pregnancy or lactation; earlier cytotoxic drug therapy; uncompensated hemolytic anemia; hematocrit less than 26% or hemoglobin less than 9 gm/100 ml; platelet count less than 80,000/mm^3; serum creatinine greater than 3 mg/100 ml; blood urea nitrogen greater than 40 mg/100 ml; creatinine clearance less than 50 ml/minute.

Three protocols were utilized in this trial. In each protocol, patients were maintained on previous doses of prednisone, and frentizole was added in a single daily dose for a predetermined length of time. Other concomitantly administered

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Table 1. Characteristics of trial patients and their therapy with prednisone, frentizole, and other drugs

Protocol, patient no.	Age/sex	Disease duration (years)	No. of criteria*	Prednisone dose mg/day		Other drug therapy (duration, months)†	Frentizole		
				Initial dose (duration, days)	Previous dose		mg/kg	mg/day	Days
A									
1	47/F	6	10	20 (114)	22	None	2.2	200	21
2	30/F	8	11	22 (60)	25	A(6), H(8)	3.0	150	21
3	47/F	5	7	15 (300)	30	M(36), P(12), H(12)	5.0	350	11
4	22/F	2	9	40 (30)	42	None	6.0	350	21
B									
5	28/F	5	6	45 (60)	30	None	4.0	225	28 + 90‡
6	35/F	8	6	20 (30)	15	A(14), H(8)	4.0	275	8 + 5
7	22/F	2	7	30 (90)	35	M(4), C(4)	4.0	250	42 + 90‡
8	25/F	3	7	30 (360)	0	None	4.0	250	42
C									
9	18/F	5	9	60 (210)	0	None	4.0	225	75
10	22/F	5	10	60 (60)	30	None	4.0	200	63 + 90‡
11	33/M	1	5	35 (120)	30	P(5), M(5), C(5)	4.0	350	63

* American Rheumatism Association criteria for the classification of SLE (8).

† A = aspirin; H = hydroxychloroquine; M = methyldopa; P = propranolol; C = chlorthalidone.

‡ After the initial course of frentizole was completed, 3 patients experienced flares of SLE. They received additional 90-day courses of therapy with frentizole, 4–6 mg/kg/day.

drugs and their doses remained constant throughout the study (Table 1). Protocol A was designed as a dose ranging study to determine the effective and/or toxic doses of frentizole. Four protocol A patients were admitted to the University of Michigan Clinical Research Center to receive frentizole for 21 days. Patient #3 experienced dysfunctional uterine bleeding on the tenth day of frentizole therapy. She was treated with progesterone and uterine dilitation and curettage, her prednisone dose was increased to 60 mg/day, and she was dropped from the study. A bone marrow examination and coagulation studies showed no evidence of frentizole toxicity. Hepatic toxicity in patient #4, who received 6 mg/kg/day, led us to reduce the dose for patients in protocols B and C to 4 mg/kg/day. Patients in protocols B and C were hospitalized in the Clinical Research Center for approximately 1 week at the beginning and for 3 days at the end of an initial course of frentizole therapy. In protocol B (Table 1), 4 patients were scheduled to receive frentizole for 42 days. However, 2 patients (#5 and #6) developed hepatotoxicity and patient #6 was dropped from the trial (described in Results). In protocol C (Table 1), 2 patients were treated with frentizole for 63 days and 1 patient received frentizole for 75 days.

In protocols A and B, doses of prednisone were not changed during frentizole therapy; however, beginning 1 week after frentizole treatment was stopped, prednisone doses could be tapered at the discretion of the investigator. In protocol C, the prednisone doses could be tapered after the initial 21 days of frentizole therapy. Patients who experienced lupus flares in the 90-day period following termination of frentizole therapy were eligible for retreatment if they met the selection criteria. Patients #4, #7, and #10 received frentizole (4–6 mg/kg/day) for an additional 90-day period (described in Results).

Each patient had pre- and posttreatment studies including chest roentgenograms, electrocardiograms, bone marrow aspirates and biopsies, and tests for delayed hypersensitivity to 0.1 ml intracutaneous injections of five skin test antigens (*Candida*, PPD intermediate strength, streptokinase plus streptodornase, dermatophyton extract, and mumps antigen). At intervals of 3–7 days during the treatment period, patients had complete blood counts, urinalyses, and measurements of serum Na, K, Cl, HCO_3, blood urea nitrogen, creatinine, calcium, phosphorus, glucose, albumin, uric acid, bilirubin, alkaline phosphatase, serum glutamic pyruvate transaminase (SGPT), serum glutamic oxaloacetic transaminase (SGOT), lactic acid dehydrogenase (LDH), and triglycerides. Twenty-four hour urine content of creatinine and protein was measured weekly. At intervals of 1, 2, or 4 weeks, the following tests were obtained: serum IgG, IgM, IgA, rheumatoid factor (latex agglutination method), direct Coombs test, indirect immunofluorescent antinuclear antibody test in

Table 2. Criteria for selection of trial participants

1. Four or more ARA classification criteria for SLE (8)*
2. Two or more clinical manifestations of active SLE present for at least 30 days:
   a. appearance or progression of SLE rash
   b. appearance or progression of cutaneous vasculitis
   c. unexplained (nonbacterial) fever (> 37.8°C)
   d. pleurisy or pericarditis
   e. severe myalgias, arthralgias, or synovitis
   f. appearance of proteinuria greater than 2 gm/24 hours
3. Serum total hemolytic complement activity less than 80 CH50 units (normal 104–188) (9) and/or antiDNA antibody levels greater than 30% (normal 0–20% binding in modified Farr assay) (10)
4. Stable prednisone dose of 15 mg/day or greater for at least 30 days
5. Presence of corticosteroid side effects

* ARA = American Rheumatism Association.

Table 3. Clinical findings of active SLE in 9 patients treated with frentizole

		End of therapy				After end of therapy (1 month)			
	Before*	Worse	Better	Absent	Unchanged	Worse	Better	Absent	Unchanged
Skin†	8	0	4	2	2	0	3	3	2
Mucosa‡	4	0	0	3	1	0	0	3	0
Pleurisy	1	0	0	1	0	0	0	1	0
Joints¶	9	1	4	1	3	1	4	1	3

* Numbers in table are numbers of patients.
† Reappearance or progression of discoid lesions, other SLE rash, and/or cutaneous vasculitis.
‡ Oral or nasal mucosal ulcerations.
¶ Signs of joint inflammation.

titered serum, antiDNA antibody (by modified Farr technique), CH50, C3, C4, thyroid antibodies, T and B lymphocyte enumeration (sheep red blood cell rosette formation and direct immunofluorescence of surface immunoglobulins, respectively), and lymphocyte stimulation assays with phytohemagglutinin, pokeweed mitogen, and concanavalin A. *P* values were derived by application of the paired *t* test.

Each patient was examined by one of the investigators (TVV, SEW, DRK) at least once a week during the trial.

RESULTS

Nine patients completed at least one 21-day course of frentizole. Table 3 records signs of clinical SLE activity before and after an initial course of frentizole therapy. Clinical improvement was noted in 8 of the 9 patients. Figure 1 summarizes serum DNA binding values before, at the end of the initial course, and at 1, 4, and 5 months after completion of the initial course of frentizole therapy. The mean value at the beginning of treatment was 47%. After the treatment period, mean DNA binding fell to 34% ($P < 0.05$). In 7 of the 9 pa tients, decreased levels of DNA binding persisted for at least 1 month after frentizole therapy was discontinued.

Mean serum CH50 values before and after treatment are presented in Figure 2. At the end of the initial course of frentizole therapy, mean CH50 had increased from 101 to 120 CH50 units ($P < 0.025$). One month after frentizole therapy was stopped, mean serum hemolytic complement activity was 127 CH50 units. The largest increases in CH50 levels were noted in the patients who had abnormally low pretreatment levels (patients #1, 2, 7, 10, 11). CH50 levels in these patients increased from a mean pretreatment value of 73 to 112 after the initial course of frentizole ($P < 0.001$), and increased CH50 was maintained during the subsequent month. Changes in mean levels of C3 and C4 (Table 4) paralleled changes in CH50 levels.

Mean serum levels of IgG decreased following frentizole therapy, while IgA and IgM levels remained unchanged.

No patient became leukopenic during or after frentizole therapy. One patient (#2) had a low leukocyte count of 3,750 cells/mm^3 at the beginning of treatment. Subsequently, the leukocyte count increased during treatment to 4,250 cells/mm^3. One month after frentizole therapy was stopped, the leukocyte count was 5,250 cells/mm^3. Although total white blood cell counts remained essentially stable in all patients, total lymphocyte counts decreased in 7 of 9 patients. The mean lym-

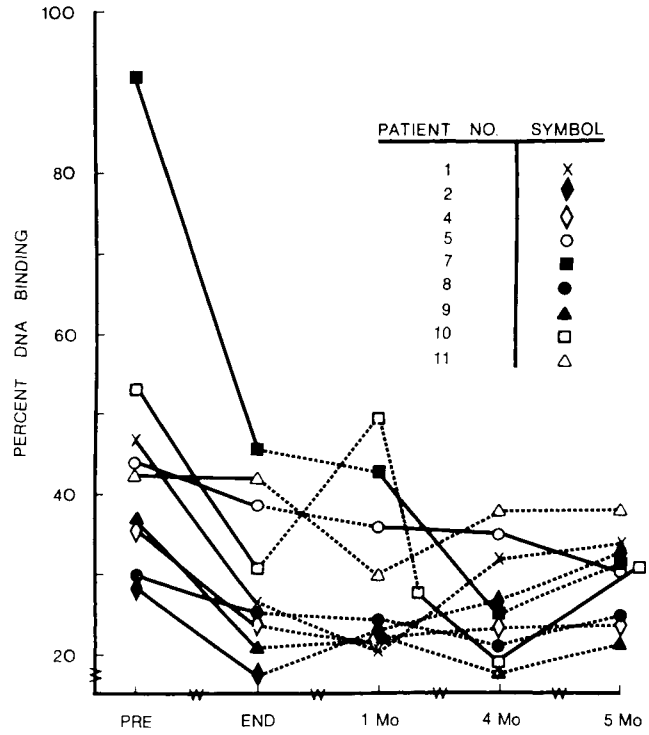

Figure 1. This graph illustrates DNA binding immediately before frentizole therapy, at the end of the initial 21- to 75-day course, and 1, 4, and 5 months after completion of initial course of frentizole. Solid lines represent times the patients were receiving frentizole and broken lines indicate times the patients were not receiving this drug. Each point on the graph represents the mean of two determinations.

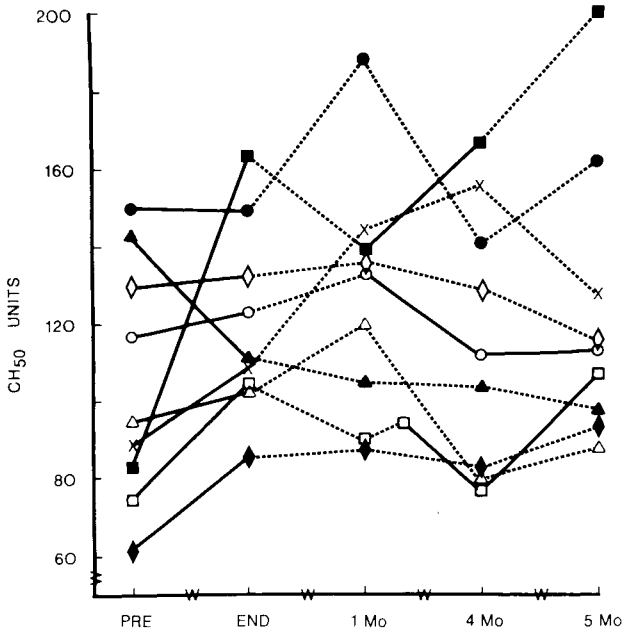

Figure 2. CH50 levels for the 9 SLE patients who completed at least one course of frentizole therapy. This figure illustrates CH50 immediately before frentizole therapy was started **(PRE)**, at the end of the initial 21- to 75-day frentizole course **(END)**, and 1, 4, and 5 months after completion of the initial course of frentizole. Solid lines represent times the patients were receiving frentizole and broken lines indicate times the patients were not receiving this drug.

phocyte count decreased by 25% during frentizole therapy, and this was maintained for the month following treatment (Table 4). Mean granulocyte counts increased in proportion to the decrease in mean lymphocyte counts.

Decreases in serum antinuclear antibody titers in 7 of the 9 patients paralleled decreases in serum DNA binding activity. Frentizole therapy was not associated with changes in Coombs tests or rheumatoid factor titers. No consistent changes were noted in responses to skin test antigens and no patient became anergic during or following treatment. Peripheral B cells and T cells were not decreased, and consistent changes in lymphocyte mitogenic responses were not noted. Chest roentgenograms, electrocardiograms, bone marrow aspirates, urine sediments, and creatinine clearances were unchanged. Infections did not develop in any of the patients during or following frentizole therapy. There was no evidence of toxicity involving bone marrow, peripheral blood, or thyroid. Hepatotoxicity was detected in 3 patients (discussed below).

Figure 3 depicts prednisone doses over a minimum period of 7 months for each of the 9 patients who completed at least one course of frentizole. Alterations in doses were guided by the investigators' assessments of disease activity and utilized clinical findings as well as serologic parameters (DNA binding activity and serum levels of CH50). The prednisone doses were reduced in 8 of the 9 patients during and following frentizole therapy.

Hepatotoxicity in association with frentizole therapy appeared in 3 of the 11 patients who participated in this study. This complication was detected in each by an abrupt increase in the serum levels of SGPT and SGOT occurring 11 to 25 days after initiation of treatment. Patient #4 had normal SGPT, SGOT, and LDH values after 14 days of therapy with frentizole, 6 mg/kg/day. Four days later SGPT was 2200, SGOT was 71, and LDH was 271 IU/liter. Frentizole was stopped on day 21. SGOT and LDH levels returned to the normal range within 7 days, and SGPT returned to normal 34 days after the drug was stopped. During the 6 months following this study, patient #4 remained in clinical and serologic remission and the prednisone dose was decreased from 40 to 11 mg/day. Patient #5 experienced hepatotoxicity and had an elevated SGPT value (264 IU/liter) on the twenty-fifth day of therapy with frentizole, 4 mg/kg/day. The drug was stopped on day 28; at that time, SGOT was minimally elevated (38 IU/liter). Thirty-two days after frentizole was discontinued, SGPT returned to normal. Patient #5 was subsequently retreated with frentizole for 6 months and no hepatotoxicity was observed. Patient #6 developed fever, ma-

Table 4. Complement, immunoglobulin, and peripheral blood leukocyte levels before, at the end, and 1 month after frentizole therapy in 9 patients with SLE

	Before*	End	One month after end
C3	85.0 ± 2.0	109.0 ± 2.0†	107.0 ± 1.0†
C4	14.0 ± 1.0	19.0 ± 1.0‡	20.0 ± 1.0‡
IgG	1020.0 ± 6.0	966.0 ± 7.0	950.0 ± 6.0§
IgM	167.0 ± 2.0	160.0 ± 2.0	163.0 ± 2.0
IgA	288.0 ± 2.0	288.0 ± 2.0	296.0 ± 2.0
Leukocytes	9.2 ± 1.0	9.4 ± 1.1	9.2 ± 0.9
Lymphocytes	2.3 ± 0.4	1.7 ± 0.3	1.8 ± 0.3
T lymphocytes	1.1 ± 0.2	0.8 ± 0.2	0.9 ± 0.2
B lymphocytes	0.1 ± 0.05	0.1 ± 0.02	0.1 ± 0.03
% T lymphocytes	51.8 ± 2.7	41.9 ± 4.2	51.7 ± 6.3
% B lymphocytes	5.8 ± 1.2	8.7 ± 2.8	6.9 ± 1.9
Platelets	270.0 ± 99.0	311.0 ± 118.0‡	287.0 ± 100.0

* Mean ± SE. Normal values: C3 99–192, C4 17–49, IgG 564–1765, IgM 53–375, IgA 85–385 mg/100 ml; leukocytes 4.0–10.0, lymphocytes 0.8–5.0, T lymphocytes 0.5–3.6, B lymphocytes 0.02–0.4 × 10^3 cells/mm^3; % T lymphocytes 57–72, % B lymphocytes 2–9; platelets 200–400 × 10^3 cells/mm^3.

† Compared to pretreatment value, $P < 0.001$.

‡ Compared to pretreatment value, $P < 0.05$.

§ Compared to pretreatment value, $P < 0.025$.

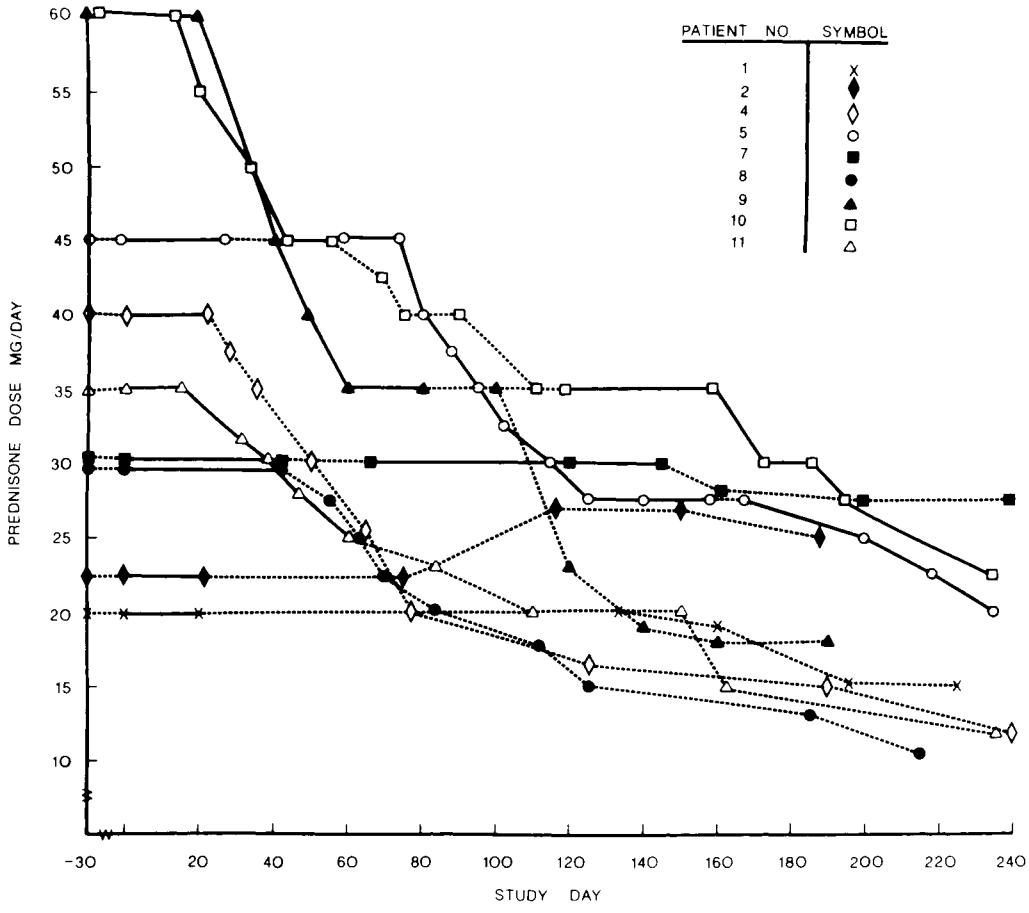

Figure 3. Daily prednisone doses for each of the 9 SLE patients who completed at least one course of frentizole. Solid lines represent times the patients were receiving frentizole. Broken lines indicate periods when frentizole was not given.

laise, nausea, and diarrhea on day 8 of treatment and she elected to discontinue the drug. Three days later, her SGPT, SGOT, and LDH levels rose to 665, 393, and 540 IU/liter, respectively. The patient's symptoms subsided after 4 days, and SGOT and LDH values returned to normal 16 days after frentizole was stopped. During retreatment with frentizole, definite increases in SGPT, SGOT, and LDH levels were seen. Frentizole therapy was stopped, and liver function tests returned to normal after 16 days. These 3 patients had no previous history of aspirin-induced hepatitis or other liver disease. In each case, tests for the presence of hepatitis B surface antigen and antibody to hepatitis B surface antigen were negative. Liver biopsies were not performed.

Three patients (#5, 7, and 10) were retreated with frentizole after clinical and serologic SLE activity appeared one or more months after the completion of the initial course of therapy. One month after frentizole was discontinued, skin rash, synovitis, and elevated serum DNA binding (39%) were observed in patient #5. After 90 days of additional treatment, there was no clinical SLE activity, and the daily prednisone dose had been tapered from 45 to 27.5 mg/day (Figure 3). The patient continued to receive frentizole at a daily dose of 250 mg in a separate protocol for an additional 98 days. A further decrease in prednisone dose was achieved (Figure 3), and there was no evidence of recurrent hepatotoxicity. Patient #7 was also retreated with frentizole for an additional 90 days. One year before the study began, she was treated with prednisone, 60 mg/day to control biopsy-proven diffuse proliferative glomerulonephritis. Prednisone was tapered to 30 mg/day, and a lupus flare occurred with cutaneous vasculitis, synovitis, elevated serum DNA binding (93%), depressed CH50 (82 CH50 units), hematuria, and nephrotic syndrome. During the initial course of frentizole

therapy, cutaneous vasculitis resolved. DNA binding fell to 38%, and CH50 increased to 155 CH50 units. A second course of frentizole therapy was not associated with clinical or serologic toxicity. Creatinine clearance was unchanged, proteinuria decreased from 6.5 to 0.9 gm/24 hours, hematuria decreased, and clinical improvement was maintained. Patient #10 was the third patient to receive a second course of frentizole therapy. When she first entered the study, the prednisone dose was 60 mg/day. Signs of active SLE included a malar rash, cutaneous vasculitis, oral ulcers, and synovitis. During 63 days of frentizole therapy, the skin lesions, oral ulcers, and synovitis resolved. DNA binding decreased from 56 to 30%, and CH50 increased from 74 to 106 CH50 units. The prednisone dose was tapered to 45 mg/day. Six weeks after frentizole therapy was stopped, the malar rash, cutaneous vasculitis, and synovitis reappeared. Frentizole therapy was restarted at a dose of 4 mg/kg/day and later increased to 6 mg/kg/day. The skin lesions and synovitis resolved, antiDNA was 31%, and CH50 increased to 111 units. The prednisone dose was reduced successfully to 15 mg/day. Frentizole toxicity was not observed.

DISCUSSION

This report describes the first Phase II open label trial of frentizole in patients with active SLE. The protocols were designed to permit ethical evaluation of frentizole in active SLE patients who were taking toxic but ineffective daily doses of prednisone. Nine of the 11 patients who entered this trial completed an initial course of frentizole and therefore represent cases that could be evaluated concerning the potential therapeutic efficacy of this drug.

Clinical improvement was noted in 8 of the 9 patients who completed an initial course of frentizole. Favorable changes in clinical and laboratory parameters of active SLE were first detected 17 to 39 days after the experimental drug was given. Cumulative doses at the times of improvement ranged from 3.2 to 8.7 gm.

Frentizole and cortisol were synergistic in suppression of mouse antibody response to sheep red blood cells (5). It cannot be concluded that similar synergism occurred in the patients who participated in this trial. However, the significant reductions in mean prednisone dosage which were achieved during and after frentizole therapy suggested that this drug might have a steroid-sparing effect.

Frentizole therapy did not decrease autoimmune responses consistently in patients with active SLE. Decreases of DNA binding, ANA titers, and serum IgG levels during the initial 21- to 75-day courses of therapy may have resulted from spontaneous improvement of disease or concomitant administration of prednisone. Frentizole therapy did not depress cell mediated immunity. There was a trend to suppression of peripheral lymphocytes and T lymphocytes in patients treated with frentizole; however, skin test responses to a standard battery of antigens were not decreased. Furthermore, frentizole therapy did not correlate with changes in lymphocyte responses to mitogenic stimulation. Our experience was not consistent with the findings of other investigators who reported that in vitro incubation of human lymphocytes with frentizole inhibited blastogenic responses to phytohemagglutinin, pokeweed mitogen, and concanavalin A (11).

Cytotoxic drugs such as cyclophosphamide, chlorambucil, and azathioprine may induce leukopenia or thrombocytopenia. These complications have not been found in humans (5) treated with frentizole. Furthermore, results of animal studies suggested that frentizole in immunosuppressive doses did not impair host resistance to bacterial, fungal, and viral infections as much as cytotoxic immunosuppressive drugs (6). In this respect, the absence of infections during and after frentizole therapy in the 11 SLE patients of this study may be noteworthy.

Frentizole-associated hepatic toxicity was noted in 3 of the 11 patients who participated in this trial. The mechanism by which frentizole caused hepatotoxicity is unknown. This drug is metabolized rapidly by the liver (12), and it is suspected that frentizole induces idiosyncratic hepatitis similar to that experienced by some patients with SLE who take aspirin (13). No other toxic effects were detected in this short-term trial. However, long-term use of frentizole in humans may lead to hematologic, hepatic, or thyroid toxicity similar to that observed in animal toxicity studies.

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