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Clinical Trial with Clofazimine for Treating Erythema Dyschromicum Perstans

Evaluation of Cell-Mediated Immunity

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ABSTRACT: Eight patients were studied to determine the possible use of clofazimine for treating erythema dyschromicum perstans (EDP). The T-helper/T-suppressor cytotoxic ratio (CD-4/CD-8) and the in vitro lymphoproliferative response on stimulation with phytohemaglutin (PHA) and concanavalin A (Con A) were determined in peripheral blood before and after treatment. Of the eight patients studied, seven had excellent to good responses, whereas only one had a marginal response. The immunologic evaluation before and after treatment showed a significant change in the CD-4/CD-8 ratio, a decrease of the response to PHA, and no change in the response to Con A. The results obtained show that clofazimine is useful for treating this nosologic entity because of its cosmetic effect, and also because it induces changes in cell-mediated response, which could be very important therapeutically.

Ashy dermatosis or erythema dyschromicum perstans (EDP) is a chronic skin disorder characterized by a dyschromia that varies from ash-gray to brown, and is distributed all over the body, forming asymmetric confluent areas of different sizes.[1,2] Initially, they show erythematous borders to be discretely elevated, which has been associated with signs of activity.[2]

Currently there is no treatment for this disease, although many medications have been tried: sun shields, keratolytics, antibiotics in all their forms, steroids, antihistamines, vitamins, diaminodiphenylsulphone (DDS), isoniazide, griseofulvin, autohemotherapy, chloroquine, psychotherapy, estrogens, and placebos, among others.[3-7]

A drug that is commonly used in antihanseniasis therapy, clofazimine,[8] has as active component an immunophenazinic dye. This substance tends to accumulate in fatty tissues and in the reticuloendothelial cells, where it can be ingested by macrophages. In humans, it produces a reddish coloring of the skin. Due to this characteristic, we decided to try it in patients with EDP to evaluate whether it would produce a uniform coloring of the skin that perhaps would mask the unaesthetic areas.

The initial clinical experience included five patients with EDP who were treated with clofazimine for at least 3 months. Three had excellent results.

Due to these stimulating results, we considered the possibility that the beneficial effects obtained were not only due to camouflage of the lesions, but that also the immunologic mechanisms possibly involved in the development of this disease had been modified by the drug. Therefore, a protocol was designed to study the use of clofazimine in patients with EDP, and to evaluate the clinical and immunologic aspects.

Patients and Methods

Patients

Eight patients ranging in ages from 11–43 years (mean, 20.9 years) were studied. They had not received medication for at least 9 months before entering the trial. Seven were female (87.55%) and one was male (12.25%). Their skin color according to Fitzpatrick's scale was as follows: skin color types IV and V, 6 patients (62.5%); skin color types II and III, 2 patients (25.0%); and skin color type I, 1 patient (12.5%). The

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TABLE 1. *Improvement Scale*

'aluation	Physician's Evaluation
ood	++++: cure (the skin had a uniform coloring).
	+++: good improvement (there was a discrete difference in hue between normal skin and skin previously compromised).
'ate	++: moderate improvement (lesions persisted, but borders became diffuse).
	+: poor response (lesions and borders persisted).

of disease varied between 11 months and 6 ean, 3.5 years).

aminations

iopsy specimens were taken from an appar- althy area of the skin and from the border of a esion and were histopathologically examined. lymphocyte transformation test (LTT) with d Con A, using a microtest technique accord- :astes et al.,[9] was carried out. To determine iocyte subpopulations, an immunocytochem- cedure was performed using avidin-biotin- ase complex (ABC) according to the method enti et al.[10] Specific monoclonal antibodies ;ed for CD-4- and CD-8-bearing T-lympho- Other complementary tests also were per- All of the tests were repeated after treatment npleted.

nt Scheme

zimine: Patients weighing less than 40 kg re- 100 mg orally on alternate days. Patients over ceived 100 mg/d in a single dose. This scheme owed for 3 months, after which the dose was ed to 200 mg/wk and 400 mg/wk, respec- according to weight. Clinical, photographic,

TABLE 2. *Improvement Evaluation*

nt's Evaluation		Physician's Evaluation	
n	No. of Patients	Evaluation	No. of Patients
	3	++++	3
	4	+++	3
e	0	++	1
	1	+	1
	8		8

TABLE 3. *Cell Mediated Immunology Evaluation of EDP Patients Before and After Clofazimine Treatment*

Therapy	CD4/CD8 Relationship	PHA 12.5 mg/well	Con A 2.5 mg/well
Without	1.51*	43.5†	10.9
Treatment	±0.16‡	±1.1	±2.7
With	1.1	144*	12.5
Treatment	±0.12	±25.7	±2.9

* $p < 0.05$ when compared with treatment.
† $p < 0.005$ when compared with treatment.
‡ Standard error.

and laboratory controls were repeated monthly for evaluation of the response to therapy and possible adverse side effects. LTTs and determination of CD-4/CD-8 ratios were repeated after 3 months. During the clinical evaluation, both patients and the physician made a subjective analysis of improvement according to the scale shown in Table 1.

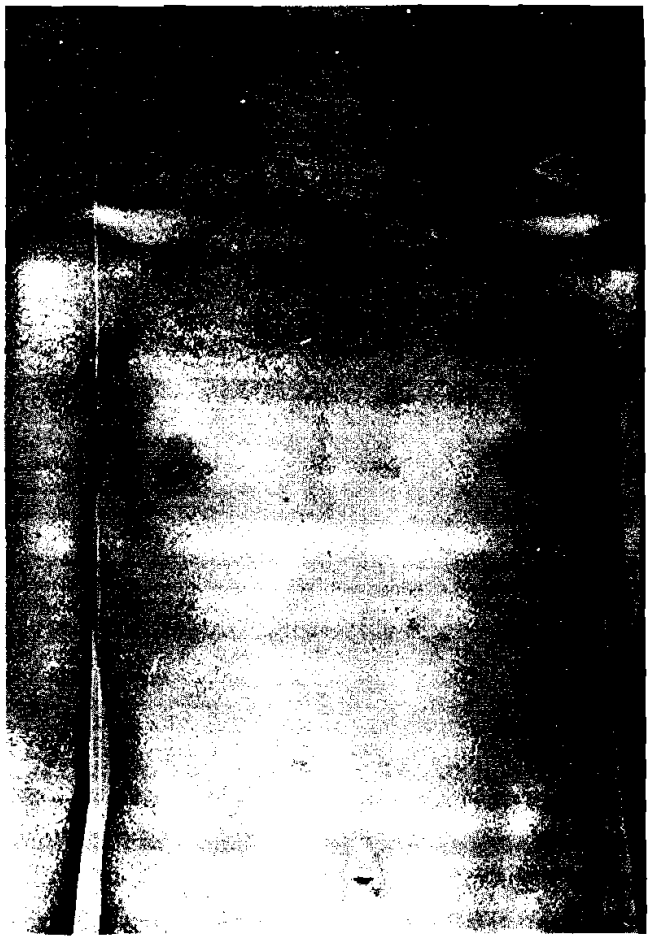

FIG. 1. Patient before clofazimine.

Results

Of the eight patients included in the group, one left treatment before 2 months due to lack of clinical improvement. The other seven followed the therapy regimen regularly during a period that varied from 3 to 8 months. All patients showed improvement with respect to their lesions (Figs. 1, 2). Improvement ranged from complete cure to evident decrease both in the patient's and the physician's evaluation, as shown in Table 2.

Seven patients had side effects: reddish hue of the skin, 7 patients; epigastralgia, 2 patients; cutis xerosis, 1 patient. In no case was therapy discontinued due to side effects. There were no changes in the laboratory parameters evaluated. Table 3 shows the results of the cell-mediated immunity tests.

The CD-4/CD-8 ratio decreased in patients after treatment with clofazimine. In LTTs, lymphocyte response to PHA was significantly higher after treatment, whereas there was no variation in the response to Con A.

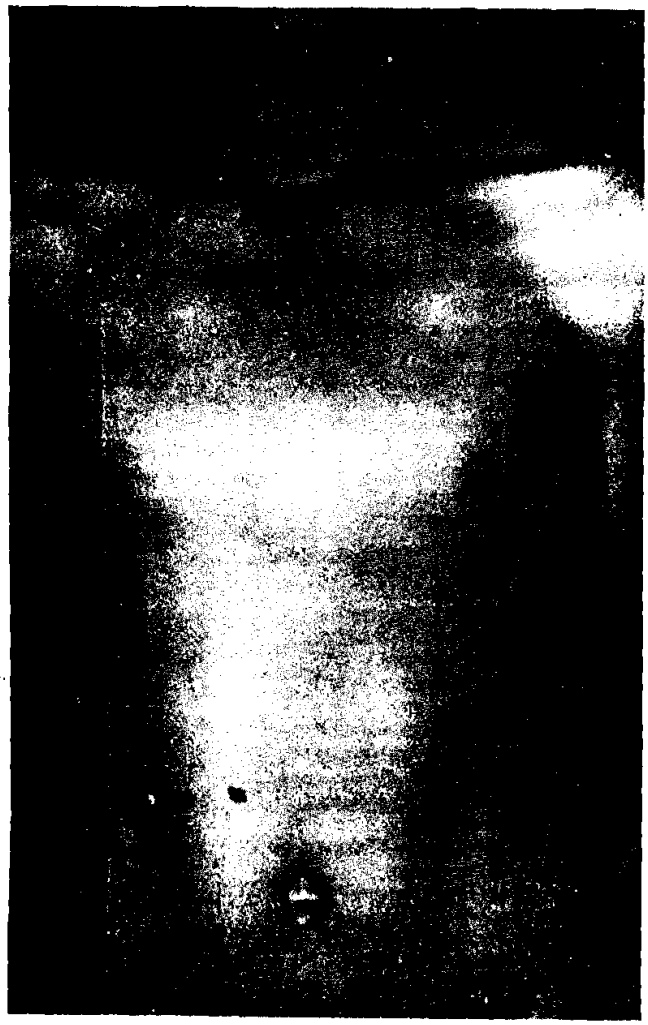

FIG. 2. Patient after clofazimine.

Discussion

This trial has shown that clofazimine can be an effective treatment for EDP, because in seven of eight patients treated there was marked improvement. The authors continue evaluating the patients and increasing the number of persons involved in the study to corroborate the information obtained and determine whether the improvement is maintained or whether it disappears when the reddish skin hue is lost.

There have been no important adverse side effects with this treatment, suggesting that clofazimine is apparently a safe drug to use in this disease.

In recent studies (11) the possibility has been presented that the immune system participates in the development of EDP. Our findings show changes in T-lymphocyte subpopulations and in LLT responses to mitogens after treatment with clofazimine. This suggests that clofazamine might have a modulating effect on cell-mediated immune responses. This, together with the good therapeutic response obtained, suggests that there might be participation of an immune down-regulation component in this disease, which could be corrected or modified using clofazimine.

Drug Names

clofazimine: Lamprene

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