

Treatment of Moderately Severe Erythema Nodosum Leprosum with Clofazimine—A Controlled Trial*

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The results of a controlled trial of clofazimine in the treatment of erythema nodosum leprosum in a small group of patients of various races give further confirmation of the value of clofazimine in the treatment of this complication of leprosy.

Introduction

It is beyond dispute that erythema nodosum leprosum (ENL) is one of the most serious complications of lepromatous leprosy. It frequently causes chronic discomfort and malaise, and as nerves are commonly involved there is the consequent tendency to develop more deformities. Some patients are unable to work for prolonged periods, and thereby a social problem is added to the clinical one. Hence the need for a non-toxic drug that requires minimal medical supervision, i.e., which is suitable for domiciliary use, and which enables the ENL patient to return quickly to work.

The riminophenazine derivative clofazimine (B 663, Lamprene (Geigy)) has serious claims for this purpose. First synthesized by Barry and collaborators (Barry *et al.*, 1957), it was shown by Browne and Hogerzeil (1962*a, b*) and then by numerous other workers to be highly effective in the treatment of lepromatous leprosy. Browne (1965*a*, 1966), observing that surprisingly few patients receiving clofazimine developed ENL, first reported on its possible anti-inflammatory properties, and this was subsequently confirmed experimentally by Vischer (1969). Since then this additional effect of clofazimine in suppressing ENL has been confirmed by many workers, including Hastings and Trautman (1968), Imkamp (1968) and Warren (1968). During the Ninth International Leprosy Congress in 1968 a group of workers, representing most centres with experience of the drug, met in London to discuss in detail its antimycobacterial and anti-inflammatory properties (Waters, 1969). The great majority of the reports confirmed that clofazimine possesses a clinically significant anti-inflammatory effect. However, at the Leprosy Research Unit, National Leprosy Control Centre, Sungei Buloh, the trial carried out by Pettit (1967), using 100 mg of the drug

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daily in very severe ENL, failed to confirm that clofazimine was of any significant value. Therefore we considered it important to carry out a further controlled trial, this time to assess the value of clofazimine in a higher dosage (300 mg per day) in treating somewhat less severe cases of ENL. The double-blind controlled trial here reported employed the methodology of Pearson and Vedagiri (1969) and is based principally on the premise that the effectiveness of a treatment in controlling ENL can be revealed by the concomitant reduction in the requirement of other anti-ENL drugs.

Organization of the Trial

GENERAL DESIGN

The trial was designed to assess the anti-inflammatory effect of clofazimine in treating moderately severe ENL, comparing its action with an identical placebo. All patients continued treatment with dapsone (4'4-diamino-diphenyl sulphone, DDS) throughout the trial, and in addition received clofazimine for a period of 4 weeks. The trial lasted 14 weeks, and was divided into 4 periods: (1) first control period (2 weeks), (2) first trial period (4 weeks), (3) second trial period (4 weeks), (4) second control period (4 weeks). Capsules containing clofazimine (100 mg) and placebo capsules were labelled A and B respectively, and the key as to which was which was kept in a sealed envelope; this latter was opened only after the results of the trial had been analysed. Patients were allotted randomly to treatment in the 1st trial period with capsules A or B in a dosage of 3 capsules daily. In the 2nd trial period the treatment was reversed, i.e., patients who had received capsule A in the first trial period received capsule B in the second trial period, and vice versa. The capsules were issued weekly in individual containers labelled only with the patient's name, number, and the week of the trial. Thus the doctor in charge did not know which of the 2 capsules each patient was receiving at any time during the 2 trial periods, and the patients were unaware that a placebo capsule was being used at any period of the trial.

INTAKE

This consisted of 15 patients who were selected from among those living in hospital quarters and attending the clinic in the Leprosy Research Unit. They were of both sexes (10 males and 5 females) and of several races (9 Chinese, 5 Malays, and 1 Indian), while the age range was from 17 to 67 years, 6 being aged 17 to 20 years, 8 from 21 to 45 and one 67 years old). Clinically, they all had lepromatous leprosy. Histologically, they were graded lepromatous leprosy (LL) or indefinite lepromatous (LI) according to the classification of Ridley and Jopling (1966) as modified by Ridley and Waters (1969). All had received anti-leprosy treatment with dapsone for 2 to 3 years; 14 had suffered from ENL for a period of 1 to 2 years before admission to the trial, and 1 for 6 months. The ENL was severe enough to necessitate their attendance at the out-patient clinic regularly, but none of them had received any corticosteroids during the 3 months prior to admission to the trial. According to Waters' classification of the severity of ENL (Waters, 1963), 14 of them were graded 2+ and 1 graded 1+. During the trial they were left to carry on their usual daily activities, living in their quarters or dormitories; only 2 of them required admission to the hospital ward in this period.

PRELIMINARY INVESTIGATION

Before the beginning of the trial each patient underwent complete clinical examination for both the underlying leprosy condition and the severity and distribution of ENL, and coloured photographs were taken. A full urinary examination (including tests for dapsone) and white blood-cell counts (total and differential) were carried out. The chest was X-rayed if no radiograph had been recently taken, and unless previous reports were available, skin lesions were biopsied in order to confirm both the type of leprosy and that the reaction was definitely ENL. Smears taken from 6 sites (both ear lobes and 4 skin sites) were examined to determine the bacterial index (BI) and morphological index (MI), while the lepromin skin test (Mitsuda type) and the tuberculin test (using 1 t.u. of R.T. 23) were also performed, unless this had been done within 6 months prior to admission to the trial.

THERAPY

(i) *Dapsone*. All the patients were being treated with dapsone (DDS) by mouth, 12 receiving 100 mg, 2 of them 200 mg, and 1 patient 50 mg, all twice weekly. At the beginning of the trial the dose was standardized at 100 mg twice weekly for all patients and was left unchanged throughout the trial.

(ii) *Trial capsules A and B*. Patients were seen every day in the afternoon, except on Sundays. During the 2 trial periods the appropriate capsules were issued to them daily and swallowed at once in the presence of the doctor in charge (except that the Sunday capsules were issued on Saturdays).

(iii) *Other anti-inflammatory drugs*. All the patients were examined twice weekly to record the severity of ENL, and stibophen was prescribed at this time if and as required. Paracetamol was issued twice weekly to be taken freely by the patients. No other ENL drugs were prescribed during the trial.

ASSESSMENTS AND INVESTIGATIONS DURING THE TRIAL

Every day in the afternoon, except Sundays, each patient's temperature was taken and twice weekly the doctor in charge assessed the severity of the ENL. Every week the amount of stibophen prescribed for each case and the number of paracetamol tablets taken by the patient during the previous week were recorded. Once a month leucocyte counts (total and differential) and full urine examination were carried out.

Results and Comments

The results were analysed only after the end of the trial, the score being calculated according to the scheme shown in Table 1. It will be noted that in every case the higher the score, the more severe was the ENL. Results from only 10 of the patients were considered as the other 5 failed to complete the trial for social reasons, 4 because of absence for religious festivals and 1 because of urgent discharge on social grounds.

The overall results (total scores of all patients) are shown in Table 2. Comparison of the first and last columns shows that there was, on average, a slight improvement in the severity of the ENL at the finish as compared with that at the start of the trial—but the scores for all parameters during the period of clofazimine administration were markedly lower than those for the placebo

TABLE 1
Method of scoring of the assessments

Assessment	Score				
	0	1	2	3	4
ENL ^a	No	Mild	Moderate	Severe	Necrotic
Temperature	Below 99° F (37.2°C)	99°-99 ⁸	100°-100 ⁸	101°-101 ⁸	102° and above (38.9°C)
White blood-cell count	Below 10,000 per mm ³	10- 14,000	14,100-18,000	Above 18,000	
Stibophen	The score comprises the number of ml prescribed in the appropriate time period				
Paracetamol	The score is the total number of tablets taken voluntarily by the patient in the appropriate time period				

^a Grading of ENL

- Mild = few or moderate number of lesions, indolent or slightly active, no discomfort.
- Moderate = moderate number of lesions, active with slight discomfort.
- Severe = very active lesions with marked discomfort and malaise.
- Necrotic = very severe ENL with pustule formation or necrosis of the lesions.

TABLE 2

Total scores of all cases for the 5 methods of assessment throughout each study period

Assessment	First control period (2 weeks)	Placebo period (4 weeks)	Clofazimine period (4 weeks)	Second control period	
				1st 2 weeks	2nd 2 weeks
Clinical severity of ENL	54	83	48	41	38
Temperature	22	34	19	22	19
White blood-cell count	5	10	3	4	4
Dosage of stibophen (ml)	100	186	80	80	90
Voluntary dosage of paracetamol (no. of tablets)	393	672	340	289	262

period. It should be noted that 7 of the 10 patients received placebo capsules first, while in 3 cases the clofazimine treatment came before the placebo (Table 3). This unequal distribution arose by chance as a result of the loss of 5 of the original 15 patients in the trial.

The results of the assessments of individual patients in the clofazimine and placebo periods are shown in Table 3. It is clear that in the great majority of patients the scores were markedly lower in the period of clofazimine treatment, i.e., clofazimine was substantially more effective than the placebo in controlling ENL.

In a few cases, however, the scores were somewhat higher in the clofazimine period. Case 10 showed more fever and required more stibophen; cases 4 and 7 recorded higher scores for fever; and case 2 was graded as suffering from more severe ENL. In each instance the additional scores were incurred during the first few days of clofazimine treatment, i.e., before the drug had become fully effective. This gradual development of the ENL-suppressive effect of clofazimine is shown clearly in the histogram (Fig. 1), which also shows that the activity of the drug persisted during the week after treatment had been stopped.

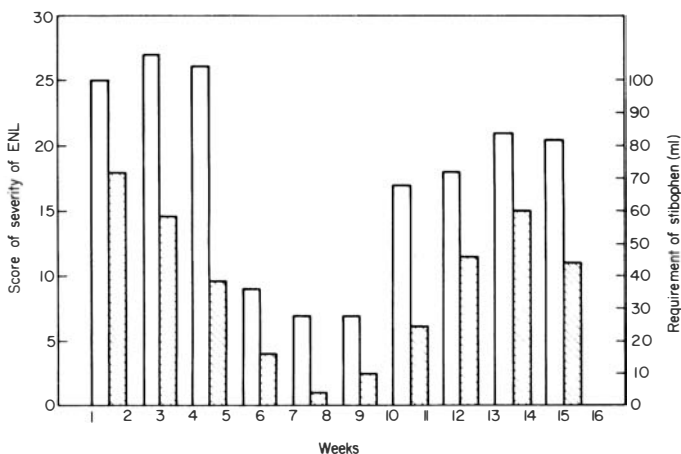


Fig. 1. Histogram showing the weekly scores (all patients) of the severity of the ENL, and of the stibophen requirements, for 10 weeks commencing 2 weeks before the clofazimine trial period and ending 4 weeks after stopping clofazimine. □, severity of ENL; ■, stibophen (ml).

The scores for fever and the white blood-cell counts were all on the low side, reflecting the satisfactory degree of control of ENL achieved throughout the trial in these patients.

The results of the urine examinations were normal throughout the trial, and in 3 patients minor abnormalities (a trace of proteinuria and a few red blood cells) disappeared during the period of clofazimine treatment. In all cases, however, the urine became pink or red after 2 to 3 weeks of clofazimine medication, and retained a pink tinge for 2 to 3 months after stopping the drug.

The usual skin discoloration (Browne, 1965*b*), which occurs wherever clofazimine is given in this dosage in pale-skinned patients, became apparent after 2 to 3 weeks. It showed initially as a pink tinge, later becoming reddish. In the

TABLE 3

*Scores of individual patients during the trial periods of placebo and of clofazimine treatment
(For method of scoring see Table 1)*

Patient no.	Severity of ENL		Stibophen requirement (ml)		Paracetamol intake (tablets)		Fever		Total white-cell count	
	Placebo	Clofazimine	Placebo	Clofazimine	Placebo	Clofazimine	Placebo	Clofazimine	Placebo	Clofazimine
*1	2	1	0	0	0	0	3	0	0	0
2	5	9	16	8	32	26	8	2	0	0
3	13	5	24	6	84	54	0	0	1	0
4	12	6	28	0	54	33	0	1	3	1
5	10	5	12	0	104	35	4	0	2	1
*6	12	6	18	12	78	32	3	1	1	1
7	10	5	32	14	100	40	1	2	2	0
8	11	8	26	12	80	40	8	3	0	0
9	3	0	24	10	90	40	0	0	0	0
*10	5	3	6	18	50	40	7	10	1	0

* Cases 1, 6 and 10 received clofazimine in the first trial period, the remainder received the placebo first.

short period of this trial the blackish hyperpigmentation which commonly develops in skin lesions after prolonged treatment did not occur. The discoloration began to fade as soon as the drug was stopped, but took 2 to 3 months to disappear completely. In regard to side-effects, 2 patients (cases nos. 3 and 10) developed nausea, vomiting and epigastric discomfort during the trial; in both instances this turned out to be on the first day of the period of clofazimine treatment. Both patients were admitted to hospital, the capsules given in divided dosage, one 3 times a day, and the symptoms settled within 3 days.

Discussion

Despite the short period of treatment with clofazimine (4 weeks) the overall results reveal a clear preference, in each of the 5 parameters measured, in favour of the trial drug as compared with an identical placebo. Therefore we are able to confirm the anti-inflammatory action of clofazimine in the treatment of ENL. The majority of our patients experienced an increased sense of well-being while taking the drug, and this was reflected not only in the reduction of fever but more especially by the fact that every patient reduced his voluntary intake of paracetamol. Therefore we consider clofazimine will prove beneficial in helping ENL patients to resume normal life. Imkamp (1968) has already shown that with long-term clofazimine therapy many of her patients were able to undertake employment inside the Liteta Leprosarium in Zambia. No serious toxic effects were encountered in the trial here reported, although 2 patients developed mild gastro-intestinal symptoms which however rapidly settled with rest and the administration of the clofazimine in divided doses. The drug-induced pigmentation remains a considerable disadvantage in our light-skinned patients, but in general clofazimine appears to be the safest and most suitable domiciliary treatment of chronic ENL, provided the precautions suggested in the postscript to the report of the Working Party (Waters, 1969) are observed.

In this trial we studied patients with less severe grades of ENL than those reported by Pettit (1967) and the dosage of clofazimine was higher, being 300 mg as compared with Pettit's 100 mg daily. These factors amply account for the different results obtained in the 2 trials. Browne (1966), Imkamp (1968), Warren (1968) and others have shown that different patients require individually determined dosages of clofazimine to control their manifestations of ENL. However, the majority of patients hitherto reported have been controlled on 300 mg daily, whereas 100 mg has often proved inadequate (Waters, 1969).

This trial differs from the majority of others so far reported in that we did not stop simultaneous treatment with dapsone, but continued it throughout in a dosage of 100 mg twice weekly by mouth. The good response to clofazimine which we have shown casts some doubt on the importance of dapsone *per se* in the pathogenesis of ENL.

The method of study and scoring employed made it possible to detect more precisely the phenomena that have previously been noted qualitatively—namely, the time lag before clofazimine becomes effective (Browne, 1966), and the persistence of its activity after treatment is stopped (Williams *et al.*, 1965; Atkinson *et al.*, 1967). However the persistence was short-lived, lasting a few days only (and therefore is only partly demonstrated in Fig. 1, as the histogram is graduated in complete weeks), whereas excretion in the urine continued for 2 to 3

months after the intake was stopped. This would support Browne's suggestion (1966) that the anti-ENL effect of clofazimine depends on the circulating, rather than the tissue, drug levels, although this point requires further study. In this connection it is worth noting that in experimental animals the minimal inhibitory concentration of clofazimine for *Mycobacterium leprae* is very low (Shepard, 1969), whereas much higher dosage is required to display an anti-inflammatory effect (Vischer, 1969).

The trial was designed to be "double blind", but it ceased to be so the moment the skin discoloration appeared, i.e., 2 or 3 weeks after starting clofazimine. This eventuality was foreseen, and it appears to be an insuperable barrier to truly double-blind studies of this drug in the treatment of ENL. No placebo giving similar coloration is available, and the suggestion that the doctor in charge of the trial should wear dark glasses during examination of the patients has obvious drawbacks and was not adopted.

The general problems involved in designing trials of drugs active against ENL have been summarized by Pearson and Vedagiri (1969) and by Waters (1971) and need not be reiterated here. An additional point to be noted however is the length of time such trials require. The present study, involving only 4 weeks of clofazimine treatment, took 14 weeks to complete. It is reassuring therefore that the ENL of these patients showed only slight differences in average severity at the beginning as compared with that at the end of the study. This means that the benefit of clofazimine is unlikely to have been due merely to the natural history of the condition, which will always resolve in time provided anti-leprosy treatment is continued.

An incidental problem which we encountered was concerned with the patients' personal lives. For example 4 of the 5 patients lost from the study were excluded from the analyses because they required periods of leave to visit their homes during religious festivals. These occur frequently in a multiracial country such as Malaysia, and it is evident that social as well as medical factors should be considered in overall trial planning.

The results of this trial fully confirm the suitability of the method proposed by Pearson and Vedagiri (1969) for the study of drugs used in the treatment of mild and moderately severe ENL. This provides a reliable and sensitive technique for obtaining an accurate measure of the effectiveness of an anti-ENL drug, and it could be used to evaluate the many unproven compounds currently employed in the treatment of ENL.

Summary

In a controlled trial, designed to be double-blind, 10 patients suffering from moderately severe erythema nodosum leprosum (ENL) were studied for a total of 14 weeks. The trial was subdivided into an initial control period of 2 weeks followed by a first trial period of 4 weeks in which either treatment with clofazimine, 300 mg daily, or identical placebo capsules was prescribed, then by a second trial period of 4 weeks in which the treatment given (clofazimine or placebo) was the reverse of that in the first trial period, and concluded with a final control period of 4 weeks. Dapsone was given throughout in a dosage of 100 mg twice weekly.

The results, based on the clinical severity of the ENL, temperature, white blood-cell count, total dosage of stibophen prescribed, and total number of

paracetamol tablets voluntarily consumed by patients in each of the 4 periods, showed clearly that the ENL improved during the period in which clofazimine was given. Of the 10 patients, 8 did not develop any signs of clofazimine toxicity (2 developed mild gastro-intestinal symptoms for the first few days on clofazimine); they were able to carry on their normal daily activities and did not require any special medical supervision. It is concluded that clofazimine is an effective drug in the treatment of moderately severe ENL, and that it is suitable for domiciliary use.

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