Efficacy of Clofazimine in the Prophylaxis and Suppression of Reactive Phases of Lepromatous Leprosy[1, 2]

A. B. A. Karat, Anbu Jeevaratnam, S. Karat and P. S. S. Rao[3]

The efficacy of clofazimine (Lamprene; G30, 320; B663), in severe *erythema nodosum* (E.N.L.) in lepromatous leprosy was reported in a previous communication (1). Patients from that study whose initial reaction was controlled with clofazimine or the control drug (prednisolone) and who remained free of reaction for twelve weeks thereafter were entered into another continuing study designed to determine:

1. the recurrence of reactional episodes in patients whose initial reactions were controlled for a period of three months with either prednisolone or clofazimine;
2. whether continuation of clofazimine during the post-reactive phase suppressed further attacks of reaction;
3. whether E.N.L. reaction was dose-related as far as DDS is concerned, and;
4. the effects of small and large doses of DDS as compared with clofazimine in clearing the bacterial load.

The findings with respect to patients who have been observed for at least one year in the post-reactive phase are the subject of this report.

MATERIALS AND METHODS

Of the patients included in the previous trial (1) fourteen have been carefully followed up for at least one year. Eight of these patients had been on clofazimine 100 mg three times a day (t.i.d.) (Group 1) while six patients were on prednisolone regime (Group 2).

Patients entering this phase of the study were randomly allocated to four anti-leprosy therapeutic regimes:

a. DDS	5 mg	q.d.
b. DDS	25 mg	q.d.
c. DDS	100 mg	q.d.
d. Clofazimine	100 mg	q.d.

The number allocated to the various regimes are as shown in Table 1.

For each patient, determinations were made of the changes in bacterial and morphologic indices, hemoglobin, hematocrit, total proteins, albumin and globulin, body weight and in the neurological status in addition to recording the recurrence of

1 Received for publication March 11, 1971.

2 Based on studies carried out at Schieffelin Leprosy Research Sanatorium, B. O. Karigiri, Via Katpadi, N.A.S., India.

3 A. B. A. Karat, B.Sc., M.B., M.R.C.P. (Edin), M.R.C.P. (Lond), Consultant Physician, Church of South India Hospital, Bangalore-1A, S. India; Anbu Jeevaratnam, M.B.B.S., Senior House Physician, Christian Medical College Hospital, Vellore-4, S. India; S. Karat, M.B., F.R.C.S. (Edin), Assistant Professor of Orthopaedics, St. John's Medical College, Bangalore-16, S. India; P. S. S. Rao, M.A., M.P.H., F.S.S., Associate Professor of Biostatistics, Christian Medical College, Vellore-4, S. India.

TABLE 1. *Patients observed during post-E.N.L. phase*

Regime		Group 1 (Clofazimine treated)	Group 2 (Prednisolone treated)	Total studied
DDS	5 mg q.d.	2	2	4
DDS	25 mg q.d.	—	2	2
DDS	100 mg q.d.	4	1	5
Clofazimine	100 mg q.d.	2	1	3
Total		8	6	14

reactive episodes. The reactions were graded in a 4-point scale as described in the earlier communication, where 1+ indicates mild and 4+ very severe.

RESULTS

Recurrence of reactions. The reactions noticed in the two groups are summarized in Table 2. The difference between the two groups was statistically significant ($P<0.05$).

TABLE 2. *Recurrence of reactions*

Grade of reaction	Group 1 (8)	Group 2 (6)
1+	1	1
2+	—	—
3+	—	3
TOTAL	1	4

(Figures in brackets indicate number studied.)

The one patient in Group 1 who had a 1+ reaction was on DDS 5 mg q.d. and had to be given anti-inflammatory therapy. The reaction cleared after five days. Among the four patients in Group 2 who had reactions, the patient with 1+ reaction was on DDS 5 mg q.d. and of the three patients with 3+ reaction, two were on DDS 25 mg q.d., and one was on DDS 5 mg q.d. Anti-inflammatory therapy had to be given for all of these four patients. There was no recurrence of reaction in any of the patients who were on clofazimine or on DDS 100 mg in the post-reaction phase, irrespective of whether they belonged to Group 1 (clofazimine) or Group 2 (prednisolone) during the reactive phase.

Changes in Morphologic and Bacterial Indices. Practically all the patients showed reduction in Bacterial Index and Morphologic Index (Table 3). There were no significant differences between patients in the various groups in terms of degree of reduction in these indices.

Changes in hematological indices. All patients whose initial reaction had been controlled with clofazimine showed increases in their hemoglobin and hematocrit (Table 3). Among those whose reaction had been controlled with prednisolone, two showed reduction in hemoglobin and hematocrit. On the whole, hematological improvement was better in those whose initial reaction was controlled with clofazimine than in those whose initial reaction had been controlled with prednisolone, but the differences were not statistically significant.

Changes in serum proteins. In the post-reaction phase, there was a trend towards decline in total serum protein in about half the patients in Group 1 (Table 3), but a slight increase among patients in Group 2. The difference observed between the two groups was statistically significant ($P<0.05$). Except for two patients all the patients whose initial reaction was controlled with clofazimine showed a rise in serum albumin in the post-reaction phase.

TABLE 3. *Differences between final and initial readings in the two groups under trial.*

	GROUP 1		GROUP 2	
	Mean standard ± deviation	Range	Mean standard ± deviation	Range
B.I.	−0.95 ± 0.89	−0.25 to +0.62	−0.67 ± 0.57	−0.75 to +0.12
M.I.	+0.02 ± 0.08	−0.50 to +0.37	+0.23 ± 0.28	0.0 to +0.62
Hb. (g)	+1.23 ± 1.01	+0.3 to + 3.7	+0.85 ± 1.87	−0.7 to + 4.8
P.C.V. (%)	+3.75 ± 2.99	+1.0 to +11.0	+2.67 ± 5.82	−2.0 to +15.0
Se. Protein (g)	−0.48 ± 0.63	−0.1 to + 0.3	+0.05 ± 0.08	−0.7 to + 0.8
Se. Albumin (g)	+0.06 ± 0.22	−0.4 to + 0.6	+0.20 ± 0.43	−0.4 to + 1.2
Body Weight	+2.88 ± 3.75	−2.0 to + 7.0	+1.50 ± 2.43	−2.0 to + 6.0

+ = Increase − = Decrease

TABLE 4. *Changes in neurological status*

Condition	Manual muscle		Electrical		Sensory	
	Group 1	Group 2	Group 1	Group 2	Group 1	Group 2
Improved	2	2	3	2	2	—
Same	6	2	5	4	6	6
Worse	—	2	—	—	—	—
TOTAL	8	6	8	6	8	6

Changes in body weight. Five of eight patients who had been on clofazimine showed an increase in body weight of 5 kg as compared to only one of six patients who had been on prednisolone (Table 3), the differences between groups being statistically significant ($P<.05$).

Changes in neurological status. The findings are summarized in Table 4. There was no deterioration in any of the patients who had been on clofazimine, and about two-thirds of the patients showed improvement.

Of the patients who had been on prednisolone also, about a third showed improvement but two patients in this group showed clear deterioration in motor function as judged by subjective weakness and by deterioration in manual muscle tests. Differences between two groups were, however, not statistically significant.

DISCUSSION

The eight patients in Group 1 were observed for a combined total of 564 weeks during which period only one episode of grade 1+ reaction recurred. Six patients belonging to Group 2 were observed in all for a total of 373 weeks during which time five episodes of reaction were observed, two of the episodes in the same patient. This suggests that initial control of E.N.L. with clofazimine has a further advantage of reducing the rate of recurrence of reaction when the patients are put on specific anti-leprosy therapy with dapsone in the post-reaction phase, as compared with the recurrence noted in patients in whom reaction was initially controlled with prednisolone. Further, irrespective of whether the initial reaction was controlled with clofazimine or prednisolone, none of the patients on clofazimine in the post-reaction phase had a recurrence. This emphasizes the suppressive effect of clofazimine on recurrence of E.N.L. in lepromatous leprosy.

The findings do not substantiate the generally accepted idea that E.N.L. in lepromatous leprosy during treatment with dapsone is dose-related, viz. the higher the dose the greater the incidence of reaction. There has been a tendency to advocate small doses of DDS for patients with a predilection for development of E.N.L. reactions in an attempt to maintain continuous specific anti-leprosy therapy, especially since it has been shown that the minimal inhibitory dose of dapsone in the mouse foot pad infections with *M. leprae* is extremely small ([2]). The rather high incidence of E.N.L. reactions among those on low doses of dapsone may indicate that E.N.L. reactions associated with administration of dapsone follow an 'all or none' law, with no reference to the dose of the drug.

The improvement in systemic effects of chronic reactions among the patients in whom E.N.L. reaction was controlled initially with clofazimine is worth noting.

Under the conditions of this trial it can be stated that initial control of E.N.L. reaction with clofazimine has a significant prophylactic effect against subsequent recurrence of E.N.L. reaction in the quiescent phases on re-introduction of dapsone therapy.

SUMMARY

Fourteen lepromatous leprosy patients whose severe reactive episodes were controlled by clofazimine or prednisolone were randomly allocated to one of four anti-leprosy therapy groups (DDS 5 mg q.d., DDS 25 mg q.d., DDS 100 mg q.d., or clofazimine 100 mg q.d.) and further observed for a period of at least one year. Recurrence of reaction was significantly less among those whose initial reactive phase was controlled by clofazimine. A fairly high incidence of E.N.L. among those on low doses of dapsone and none among those who were given clofazimine 100 mg q.d. or DDS 100 mg q.d. may indicate that E.N.L. reactions associated with administration of dapsone follow an 'all or none' law, with no reference to the dose of the drug. There was significant improvement in some of the systemic effects due to chronic reactions in patients who had been treated earlier with clofazimine.

RESUMEN

Catorce pacientes con lepra lepramatosa, cuyos severos episodios reaccionales habían sido controlados con clofazimina o prednisolona fueron asignados al azar dentro de cuatro grupos de terapia anti-leprosa (DDS 5 mg q.d., DDS 25 mg.q.d., DDDS 100 mg.q.d. o clofazimina 100 mg.q.d.) y se siguieron observando durante un período de por lo menos un año más. La recurrencia de la reacción fué significativamente menor entre aquellos cuya fase reaccional inicial había sido controlada con clofazimina. La incidencia medianamente alta de E.N.L. entre aquellos que recibían dosis bajas de dapsona y la ninguna incidencia entre aquellos que recibían dosis bajas de dapsona y la ninguna incidencia entre aquellos que recibían clofazimina 100 mg.q.d. o DDS 100 mg.q.d. puede indicar que las reacciones de E.N.L. asociadas a la administración de dapsona siguen una ley de "todo o nada," sin referencia a la dosis de droga. Hubo una mejoría significativa de algunos de los efectos sistémicos debidos a reacciones crónicas en pacientes que habían sido tratados anteriormente con clofazimina.

RÉSUMÉ

Quatorze malades atteints de lèpre lépremateuse, ayant présenté des épisodes graves de réaction qui avaient été jugulés par la clofazimine ou par la prednisolone ont été distribués au hasard parmi quatre groupes de thérapeutique anti-lépreuse à savoir 5 mg de DDS q.d., 25 mg de DDS q.d., 100 mg de DDS q.d. ou clofazimine 100 mg q.d. Ces malades ont été observés pendant une période s'étendant sur au moins une année. Les réicdives de réaction étaient significativement moins fréquentes parmi ceux dont la phase réactionnelle initiale avait été controlée par la clofazimine. Le fait qu'une incidence relativement élevée d'E.N.L. ait été relevée parmi les malades sous doses faibles de dapsone, alors qu'aucun épisode d'erythème noveux n'ait été observé chez les patients avant reçu de la clofazimine à la dose de 100 mg q.d. ou de la DDS à la dose de 100 mg q.d., pourrait indiquer que les réactions d'ENL associées à l'administration de dapsone suivent une loi du "tout ou rien" sans relation avec la dose du médicament qui est administrée. On n'a pas noté d'amélioration significative dans certains des effets systémiques produits par les réactions chroniques lorsqu'elles surviennent chez des malades traités auparavant par la clofazimine.

Acknowledgements. We are thankful to Mr. Cyril Pratapkumar for help with the biochemical investigations, to Mr. M. A. Furness and his team for help with neurological assessments and to Mr. J. Anandaraj of the Medical Records Department. We are particularly grateful to Dr. Th. Ahrens, of Geigy, S.A., Basle, for making the drug available to us and for the financial grant to carry out the trial.

REFERENCES

1. Karat, A. B. A., Anbu Jeevaratnam, Karat, Mrs. S. and Rao, P. S. S. Double-blind controlled clinical trial of clofazimine in reactive phases of lepromatous leprosy. Brit. Med. J. **1** (1970) 198-200.
2. Shepard, C. C., Levy, L. and Fasal, P. The sensitivity to Dapsone (DDS) of *Mycobacterium leprae* from patients with and without previous treatment. Amer. J. of Tropical Medicine **19** (1969) 258-263.