INTERNATIONAL JOURNAL OF LEPROSY Volume 54, Number 3
Printed in the U.S.A.

Combined Clofazimine- and Dapsone-resistant Leprosy. A Case Report[1]

H. K. Kar, V. N. Bhatia, and S. Harikrishnan[2]

Clofazimine was first used by Browne and Hogerzeil ([2]) in the treatment of leprosy. The bactericidal effect of this drug against *Mycobacterium leprae* was shown by Colston, *et al.* ([5]) and Holmes, *et al.* ([6]). Multiplication of *M. leprae* in the foot pads of mice is inhibited by 0.0001% w/w dietary clofazimine, a dosage which amounts to 0.1 mg/kg body weight per day ([7, 9]). Clinically, the drug is administered as an oral dose of 50 mg daily or 100 mg every other day.

Browne and Hogerzeil raised the possibility of clinical clofazimine resistance after 12 months of treatment ([2, 3]), but this was not confirmed by Browne in a report on the activity of the drug after 3 years of observation ([1]). Warndorff van Diepen ([11]) reported a case of clofazimine resistance. The patient experienced a clinical and bacteriologic relapse after 7½ years of clofazimine monotherapy, and resistance to clofazimine was confirmed by mouse foot pad drug sensitivity testing.

In this paper, we present a patient with inactive lepromatous leprosy who experienced clinical and bacteriologic relapse on dapsone monotherapy. The bacilli from this patient's relapsed skin lesions showed resistance to both clofazimine and dapsone, but sensitivity to rifampin, in standard mouse foot pad drug sensitivity testing.

CASE HISTORY

In 1956, a 19-year-old male from South India was diagnosed at our institution as having lepromatous leprosy. He was initially treated with injectable dapsone in oil with a dose of 500 mg twice weekly for a period of 5 years. The patient was then treated with 300 mg of dapsone orally twice weekly for an additional 1 year. In 1962, the patient had become clinically inactive and bacteriologically negative, and stopped taking dapsone. He remained bacteriologically negative without specific antileprosy chemotherapy until 1972. At that time, he became employed as a non-medical attendant at our institute, and was advised to resume taking dapsone in a dose of 100 mg daily indefinitely. By history the patient took his dapsone regularly until June 1984, but then became irregular. In December 1984, large numbers of shiny, glistening nodules appeared on the face, all four extremities, back, and abdomen bilaterally, but asymmetrically. Skin smears at that time showed a bacterial index (BI) which averaged 4.5+ with a morphologic index (MI) which averaged 4%. The lesions had histoid characteristics clinically, but these characteristics were not confirmed histologically. Material was collected from multiple skin scrapings from these new nodules for mouse foot pad inoculation for the determination of the sensitivity of the bacilli to dapsone, clofazimine, and rifampin.

There was no evidence from the patient's history or clinical records that he had ever consumed clofazimine, rifampin, or any other antileprosy drug except dapsone. After the bacilli were taken from the mouse foot pad studies, the patient was started on supervised treatment with rifampin 600 mg daily on an empty stomach for 2 weeks, followed by 600 mg daily for 2 consecutive days each month. In addition, the patient was given dapsone 100 mg daily and clofazimine 100 mg every other day. After 6 months of treatment, most of the new nodular skin lesions had regressed completely. Skin smears at that time showed an average BI of 4.0+ and a MI of 0%.

[1] Received for publication on 18 September 1985; accepted for publication in revised form on 7 March 1986.

[2] H. K. Kar, M.D., Assistant Director (Clinical); V. N. Bhatia, M.D., Director and Head, Division of Laboratories; S. H. Harikrishnan, B.Sc., Animal Supervisor (ICMR), Central Leprosy Teaching & Research Institute, Chingleput, Tamil Nadu 603001, India.

Reprint requests to Dr. Kar at his present address: H. K. Kar, M.D., Dermatologist, Department of Skin and S.T.D., Dr. R. M. L. Hospital, New Delhi 110001, India.

THE TABLE. *Mouse foot pad drug sensitivity test results.*

Month of harvest	Controls	Dapsone		Clofazimine		Rifampin	
		(0.01%)	(0.001%)	(0.01%)	(0.001%)	(0.03%)	(0.003%)
5	26.9[a]	Neg.[b]	29.0	Neg.	18.4	Neg.	Neg.
7	43.4	20.3	60.0	12.2	30.9	Neg.	Neg.
9	48.0	25.6	52.0	14.5	26.5	Neg.	Neg.

[a] All harvest numbers of bacilli are given as the values $\times 10^4$, i.e., $26.9 = 26.9 \times 10^4$ bacilli per foot pad.
[b] Neg. = no bacilli detected ($<0.62 \times 10^4$).

MOUSE FOOT PAD STUDIES

Locally bred Swiss albino mice were inoculated in both hind foot pads with 10^4 *M. leprae* from the multiple skin scrapings from the skin nodules of the patient. The preparation of the inoculum, the inoculation of mice, the harvesting of bacilli from the foot pad tissues, and the counting of the harvested organisms were performed according to methods reported by Shepard ([8]) and Shepard and McRae ([10]). Drugs were mixed with locally available powdered feed and fed continuously to the animals, beginning the day following foot pad inoculation of the bacilli. Clofazimine (Geigy, Manchester, U.K.) was obtained through the courtesy of M. J. Colston, London. Dapsone (Burroughs Wellcome, Bombay, India), rifampin (CIBA-GEIGY, Basel, Switzerland) and clofazimine were given in the concentrations indicated in The Table. Foot pads from two mice were harvested from the control group receiving drug-free diets and from each of the drug-treated groups at 5, 7, and 9 months following inoculation of the bacilli. As indicated in The Table, the bacilli multiplied in mice fed dapsone and clofazimine, but not in animals receiving rifampin.

DISCUSSION

In this paper, we report a lepromatous leprosy patient who relapsed with bacilli which were resistant to both clofazimine and dapsone as determined by mouse foot pad drug sensitivity testing. The patient was on dapsone monotherapy prior to relapse, but there was no history of his ever having taken clofazimine.

These results suggest that the patient's relapse was due to the development of secondary resistance to dapsone. The finding that bacilli from this patient were also capable of multiplying in mice fed continuously with diets containing 0.01% and 0.001% w/w clofazimine indicates that the bacilli were also resistant to clofazimine. One can only speculate as to how this patient's bacilli became clofazimine resistant.

One possibility is that the patient's bacilli could have originally been resistant to clofazimine, i.e., before he began dapsone treatment in 1956. Although knowledge of clofazimine sensitivity patterns of wild strains of *M. leprae* is not extensive, it is generally considered that the bacilli can be inhibited with 0.001% dietary clofazimine. A second possibility is that the patient might have been re-infected with a clofazimine-resistant strain of *M. leparae* at some time after he began treatment with dapsone. This would seem unlikely because to date there are no cases with clinically apparent secondary clofazimine-resistant leprosy in this area. Nevertheless, this patient was employed at our hospital and was in close contact with multibacillary patients being treated with clofazimine. For over ten years, clofazimine has been used here in combination with dapsone or in combination with dapsone plus rifampin. It would be possible, at least in theory, for a patient to have primary dapsone-resistant disease, develop clinically inapparent secondary clofazimine resistance while being treated with clofazimine plus dapsone, and then to transmit these bacilli to our patient-employee. A third possibility, in this strain of *M. leprae,* is that there was a cross-resistance between dapsone and clofazimine. This also seems unlikely. There are no previous reports of this phenomenon, and many cases with dapsone-resistant disease have responded well to clofazimine monotherapy in the past.

Regardless of the origin of the clofazimine-resistant bacilli in this patient, two practical points emerge from these observations. It would seem essential to test the

susceptibility of bacilli from patients admitted into chemotherapeutic clinical trials for sensitivity to all commonly used antileprosy drugs, including clofazimine. Secondly, it may be advisable to carry out surveys for primary and secondary resistance to clofazimine.

SUMMARY

A preliminary report is presented on the finding in a patient with lepromatous leprosy relapsing after maintaining clinical inactivity and bacterial negativity with dapsone monotherapy for a period of 23 years. Interestingly, *Mycobacterium leprae* from the fresh skin lesions revealed resistance to both clofazimine and dapsone by standard mouse foot pad testing.

RESUMEN

Se presenta el caso de un paciente con lepra lepromatosa que recayó después de 23 años de inactividad clínica y negatividad bacteriológica, a pesar del tratamiento sostenido con dapsona. El *M. leprae* de las lesiones frescas de la piel mostró resistencia tanto a la clofazimina como a la dapsona según la prueba estándar del cojinete plantar del ratón.

RÉSUMÉ

Ce rapport préliminaire traite d'un malade ayant présenté une récidive de lèpre lépromateuse après une période de 23 ans d'inactivité clinique et de bactériologie négative, au cours de laquelle il avait été traité par la dapsone en monothérapie. Il est intéressant de constater que les bacilles de la lèpre recueillis dans les lésions nouvelles se sont révélées résistant à la fois à la clofazimine et à la dapsone, ainsi qu'on a pu le mettre en évidence par des épreuves standards dans le coussinet plantaire de la souris.

Acknowledgments. We gratefully acknowledge the contributions of many colleagues of CLT&RI, especially Dr. S. Balakrishnan, Dr. P. S. Seshadri, Dr. (Mrs.) M. N. Padma, Dr. C. H. D. Vinod Kumar, and Dr. E. Baskeran. The authors are thankful to Mr. H. N. Venkataramaniah and other staff of the animal house of CLT&RI for their help in mouse foot pad inoculation study, and to Mrs. Sakuntala Dhasarathan for secretarial assistance.

REFERENCES

1. Browne, S. G. The transient reappearance of morphologically normal *M. leprae* in patients under treatment. Lepr. Rev. **38** (1967) 83–86.
2. Browne, S. G. and Hogerzeil, L. M. "B 663" in the treatment of leprosy. Preliminary report of a pilot trial. Lepr. Rev. **33** (1964) 6–10.
3. Browne, S. G. and Hogerzeil, L. M. Apparent resistance of *M. leprae* to "B 663." Lepr. Rev. **33** (1962) 182–184.
4. Browne, S. G. and Hogerzeil, L. M. "B 663" in the treatment of leprosy. Lepr. Rev. **33** (1962) 182–184.
5. Colston, M. J., Hilson, G. R. F. and Banerjee, D. K. The "proportional bactericidal test." A method for assessing bactericidal activity of drugs against *Mycobacterium leprae* in mice. Lepr. Rev. **49** (1978) 7–15.
6. Holmes, I. B., Banerjee, D. K. and Hilson, G. R. F. The effect of rifampicin, clofazimine and B. 1912 on the viability of *Mycobacterium leprae* in established mouse foot pad infection. Proc. Soc. Exp. Biol. Med. **151** (1976) 637–641.
7. Levy, L. Pharmacological studies of clofazimine. Am. J. Trop. Med. Hyg. **23** (1974) 1097–1108.
8. Shepard, C. C. The experimental disease that follows the injection of human leprosy bacilli into the foot pads of mice. J. Exp. Med. **112** (1960) 445–454.
9. Shepard, C. C. Minimal effective dosages in mice of clofazimine (B663) and of ethionamide against *Mycobacterium leprae.* Proc. Soc. Exp. Biol. Med. **132** (1969) 120–124.
10. Shepard, C. C. and McRae, D. H. A method of counting acid-fast bacteria. Int. J. Lepr. **36** (1968) 78–82.
11. Warndorff-van Diepen, T. Clofazimine-resistant leprosy; a case report. Int. J. Lepr. **50** (1982) 139–142.