

# Secondary Rifampin Resistance Following Multi-Drug Therapy—A Case Report<sup>1</sup>

Gift Norman, Geetha Joseph, Gigi Ebenezer, P. S. S. Sundar Rao,  
and Charles K. Job<sup>2</sup>

## ABSTRACT

This is the first report of secondary resistance to rifampin following MDT in a patient with prolonged, but irregular treatment. Repeated mouse foot-pad studies demonstrated resistance to dapsone after several years of monotherapy, and following subsequent MDT the studies demonstrated the development of resistance to rifampin.

## RÉSUMÉ

Nous rapportons ici le premier cas de résistance secondaire à la rifampicine chez un patient ayant reçu une polychimiothérapie (PCT) prolongée mais irrégulière. Des études répétées d'inoculations à la voûte plantaire de souris ont démontré la résistance à la dapsone après plusieurs années de monothérapie, et suivant l'institution de la PCT, ces mêmes études ont mis en évidence le développement d'une résistance à la rifampicine.

## RESUMEN

Este es el primer reporte de un caso de resistencia secundaria a rifampina en un paciente con lepra tratada con poliquimioterapia (PQT) de manera prolongada, pero irregular. Los estudios repetidos en la almohadilla plantar del ratón ya habían indicado el desarrollo de resistencia a la dapsone después de varios años de monoterapia con esta droga. Más tarde, estos estudios revelaron el desarrollo de resistencia a la rifampina siguiendo al tratamiento con PQT.

Emergence of drug resistance is a common phenomenon in anti-microbial therapy, and there is no reason to believe that drugs used in multi-drug therapy (MDT) for leprosy would be an exception. As rifampin is an irreplaceable key component of the MDT regimen, emergence of resistance to rifampin would create great difficulties for the treatment of individual patients<sup>(6)</sup>, and its widespread dissemination would pose a serious threat to reaching the leprosy elimination target<sup>(11)</sup>. In this paper we report

one patient who has developed resistance to rifampin and dapsone following 26 doses of World Health Organization recommended MDT regimen.

## CASE REPORT

A 45-year-old male reported at Schieffelin Leprosy Research and Training Center (S. L. R. & T. C.) in November 1980, with a complaint of having nodules over the trunk and buttocks and thickening of ear lobes for 6 months. The past history he gave included hypo-pigmented patches on his buttocks when he was 15 yrs old, for which he took native medicine followed by dapsone for 8 yrs. His condition improved and as he felt better, he had discontinued treatment on his own. The disease relapsed after 20 yrs when he was 43 yrs old and he reported to a private practitioner where he received anti-leprosy treatment for a short period, the details of which were not known. Once he felt better, he discontinued treatment again. Within 2 yrs, however, he found the disease progressing and reported to us.

<sup>1</sup>Received for publication on 23 August 2002. Accepted for publication 13 December 2002.

<sup>2</sup>G. Norman, M.D., Senior Specialist and Head; G. Joseph, M.D., Specialist, Department of Community Health; G. Ebenezer, M.D., Head, Department of Histopathology and Experimental Pathology; P. S. S. Sundar Rao, Ph.D., Director, Schieffelin Leprosy Research and Training Center; C. Job, M.D., Professor Emeritus, Department of Histopathology and Experimental Pathology, Schieffelin Leprosy Research and Training Center, Karigiri, Vellore, India.

Reprint requests to: Gift Norman, Head, Department of Community Health, Schieffelin Leprosy Research and Training Center, Karigiri, Vellore – 632 106, India. E-mail: oculep@vsnl.com

On examination, he was found to have multiple firm nodules all over the trunk and buttocks. The skin over his body was infiltrated. There was thickening of earlobes and loss of eyebrows. All major nerve trunks were thickened. He had anesthesia of his hands and feet but no obvious paralysis. Skin smear showed a bacterial index (BI) of 4+. Routine blood, urine, and stool examinations were within normal limits, except the hemoglobin, which was 9.7 G%. Histopathological examination of the skin was reported as lepromatous leprosy. Due to the long history of interrupted anti-leprosy treatment with dapson, a mouse foot pad (MFP) study for dapson drug sensitivity was done. Thirty-three inbred CBA mice were inoculated with *Mycobacterium leprae* suspension prepared from the skin biopsy received from the patient. The preparation of the inoculums, inoculation in mice, harvesting and counting of *M. leprae* from mouse foot pads used the same methodology as described by Rees<sup>(14)</sup>. The drugs were measured and mixed with locally available mouse feed in different concentrations. Feed containing rifampin was prepared once in 3 wks at concentrations of 0.01% and 0.003%. Twelve animals were used as controls and fed a normal diet with no drugs admixed. The MFP study reported 1 yr later revealed that the organisms were resistant to dapson in all concentrations namely, 0.01%, 0.001%, and 0.0001%.

In the intervening period, the patient was given supervised treatment with rifampin 600 mg and dapson 100 mg daily for the first 2 wks and then unsupervised dapson 100 mg daily, which he continued for 1 yr. His BI came down from 4+ to 2+ within a yr of treatment. Since the organisms were found to be resistant to dapson, clofazimine 100 mg daily was added to the dapson and rifampin, which he took for 3 yrs. His BI continued to remain at 2+ at the end of 3 yrs of combined therapy with dapson and clofazimine. Therefore, a MFP study was done for a second time in 1984, which showed no growth.

At that time the multi-drug therapy (MDT) trials of the WHO were going on at Karigiri. The patient was recruited into the study and was given regimen A, which consisted of supervised treatment with rifampin 600 mg and clofazimine 600 mg daily for 2

days, Inj. Acedapson (DADDS) 225 mg IM every 8 wks, and unsupervised treatment with dapson 100 mg daily. This regimen was continued for 2 yrs. At the end of 2 yrs of the regimen A, the BI had come down from 2+ to 0.75+ and it became negative in due course.

By this time, the patient had developed ulnar and median nerve paralysis leading to bilateral clawing of fingers. He had also developed absorption of toes on both feet. He was released from treatment in 1986.

During the next 11 yrs, the patient was followed up annually with a clinical and skin smear examinations and a motor/sensory assessment. He remained inactive with a BI of 0+ until 1997, when he reported with new skin lesions. On examination, he had diffuse infiltration of the body with nodules over the back, abdomen, left knee, left ear lobe, and left upper arm. The ulnar, median and lateral popliteal nerves were enlarged bilaterally. Absorption of fingers in both hands and toes of his right foot was present. Skin smears done on routine sites had a BI of 1.25+, but at the nodular lesions it was 5+ to 6+. He was diagnosed with relapsed lepromatous leprosy after WHO regimen A.

At this time (1997), a biopsy and MFP study was done for the third time. Three animals were used for studying drug susceptibility to rifampin. All 3 showed significant growth at a concentration of 0.003%. Mice to mice passage was done twice and also showed significant growth. Susceptibility to dapson and clofazimine was also studied. This MFP study revealed that the organisms were resistant to dapson at a concentration of 0.0001% and Rifampin at 0.003% level. No resistance to clofazimine was reported. It is interesting to note that he did not have any episode of reaction during these 11 yrs.

The patient was advised to take the WHO regimen B consisting of supervised treatment with rifampin 600 mg, clofazimine 300 mg, and dapson 100 mg once a month followed by unsupervised treatment with clofazimine 50 mg and dapson 100 mg daily.

During the next 11 months, the patient reported only twice to receive his treatment and was lost to follow-up. He was traced again in 2001, and his skin smears showed a routine BI = 0.5+. The selected sites, however, showed a BI = 5+. He is currently

receiving a supervised regimen containing clofazimine 50 mg daily, minocycline 100 mg daily, and ofloxacin 400 mg daily. The hope is that he will continue taking these drugs as long as is necessary.

### COMMENTS

The WHO Study Group introduced MDT in response to the serious threat to leprosy control posed by the widespread emergence of dapsone resistance (<sup>12</sup>). Compared to other drugs in the MDT regimen, i.e., dapsone (DDS) and clofazimine (CLO), rifampin (RMP) is far more bactericidal against *M. leprae* in mice and humans (<sup>7,8,9</sup>), and is considered the backbone of the MDT regimens (<sup>6</sup>). More than 10 million leprosy patients worldwide have completed their treatment with Multi-drug therapy (MDT) to date (<sup>13</sup>). It is remarkable that the overall relapse rate after completion of MDT has been about 0.1% per annum, and that RMP resistant leprosy has not been reported among patients treated with MD until recently (<sup>11</sup>).

Resistant *M. leprae* occur spontaneously as a result of mutational events, and are present in wild strains of bacterial populations that have never been exposed to any drug. The frequency and degree of resistance of these mutants in a wild strain depends on the origin of the strain, the drug and its concentration, and the size of the bacterial population. The development of drug resistance during treatment is probably the result of a selective process; whereas the drug kills a majority of susceptible organisms, the resistant mutants survive and multiply. Finally, the mutants replace the susceptible organisms in the population.

There are two apparent reasons why this patient developed resistance to dapsone. Firstly, the patient was initially on dapsone monotherapy for 8 yrs. Dapsone monotherapy in a multi-bacillary patient is in itself a risk factor for developing drug resistance, even though not all patients will relapse having developed drug resistant strains (<sup>5</sup>).

Secondly, drug compliance seems to have been a major problem with this patient. Though the details of his initial treatment are unclear, it is obvious that his treatment was irregular. It is well known that irregular treatment leads to low drug concentrations in blood or tissues. Low drug concentra-

tions provide an opportunity for resistant mutants to survive, and further mutate into organisms with an even higher degree of resistance (<sup>1,10</sup>).

Twenty yrs after the initial dapsone monotherapy, when the patient relapsed with organisms that were resistant to dapsone, he was given rifampin for 2 wks along with dapsone, which was continued for 1 yr. It is evident that the patient received only rifampin monotherapy during that period and it is possible that a rifampin resistant strain was induced at that time. Clofazimine was added, but it failed to bring down the BI even after 3 yrs. At that time, the patient was recruited into the WHO MDT trial, which brought down the BI to 0+. During the next 11 yrs he remained negative, but relapsed at the end of that period with organisms resistant to dapsone at 0.0001% concentration and rifampin at 0.003% concentration. It is to be noted that the earlier strain of *M. leprae* was resistant to dapsone in all concentrations.

Several factors stand out in this multi-drug resistant patient: a history of having had lepromatous leprosy for many yrs (40 yrs), an initial high bacterial index, several unusual regimens, irregular and inadequate intake of anti-leprosy therapy, and absence of any reactional episodes.

Secondary resistance to rifampin was first reported in the 1970's (<sup>4</sup>) based on patients treated with rifampin as monotherapy. Subsequently, 9 more cases of rifampin resistance have been reported (<sup>3</sup>). More recently, of 39 strains of *M. leprae* isolated from patients with multibacillary leprosy who relapsed, 22 strains were found to be resistant to rifampin (<sup>2</sup>). All rifampin resistant strains were recovered from patients who had been treated with more than 50 doses of rifampin, usually given as monotherapy. While rifampin resistance following MDT has not been reported to date, it is possible that several rifampin resistant cases following MDT have gone undetected. It is therefore recommended that resistance to rifampin following MDT be monitored in different parts of the world and information on its magnitude be gathered.

### REFERENCES

1. ELLARD, G. A. Pharmacological aspects of the chemotherapy of leprosy. *Lepr. Rev.* **46** (suppl.) (1975) 41-51.

2. GROSSET, J. H., GUELPA-LAURAS, C. C., BOBIN, P., BRUCKER, G., CARTEL, J. L., CONSTANT-DESORTES, M., FLAGEUL, B., FREDRIC, M., GUILLAUME, J. C. and MILLAN, J. Study of 39 documented relapses of multibacillary leprosy after treatment with rifampin. *Int. J. Lepr.* **57**(3) (1989) 607–614.
3. GUELPA-LAURAS, C. C., GROSSET, J., CONSTANT-DESORTES, M. and BRUCKER, G. Nine cases of rifampin-resistant leprosy. *Int. J. Lepr.* **52** (1984) 101–102.
4. JACOBSON, R. R. and HASTINGS, R. C. Rifampin resistant leprosy. *Lancet*. **ii** (1976) 1304–1305.
5. JI, B. Drug resistance in leprosy—a review. *Lepr. Rev.* **56** (1985) 265–278.
6. JI, B. Rifampin-resistant leprosy: a review and research proposal of a pilot study. *Lepr. Rev.* **73** (2002) 2–8.
7. LEVY, L., SHEPARD, C. C. and FASAL, P. The bactericidal effect of rifampin on *M. leprae* in man: (a) single doses of 600, 900 and 1200 mg; and (b) daily doses of 300 mg. *Int. J. Lepr.* **44** (1976) 183–187.
8. SHEPARD, C. C., LEVY, L. and FASAL, P. Further experience with the rapid bactericidal effect of rifampin on *Mycobacterium leprae*. *Am. L. Trop. Med. Hyg.* **23** (1974) 1120–1124.
9. SHEPARD, C. C., LEVY, L. and FASAL, P. Rapid bactericidal effect of rifampin on *Mycobacterium leprae*. *Am. L. Trop. Med. Hyg.* **21** (1972) 446–449.
10. WATERS, M. F. R. The diagnosis and management of dapsone-resistant leprosy. *Lepr. Rev.* **48** (1977) 95–105.
11. WHO EXPERT COMMITTEE ON LEPROSY. Seventh report. Geneva: World Health Organization, 1998. Tech. Rep. Ser. 874.
12. WHO STUDY GROUP. Chemotherapy of leprosy. Geneva: World Health Organization, 1994. Tech. Rep. Ser. 847.
13. WORLD HEALTH ORGANIZATION. Global leprosy situation. *Weekly Epidemiol. Rec.* **74** (1999) 313–316.
14. WORLD HEALTH ORGANIZATION. Laboratory techniques for leprosy. WHO / CDS / LEP / **86.4** (1987) 65.