Follow-up of Lepromatous (LL and BL) Patients on Dapsone (DDS) Monotherapy After Attainment of Smear Negativity in Gudiyatham Taluk, South India[1]

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Patients with lepromatous leprosy appear to show no improvement in their specific immune response to *Mycobacterium leprae* even five years after their Bacterial Index (BI) ([2]) has fallen to zero ([3]). This could mean that smear negative lepromatous patients remain susceptible to reinfection even if chemotherapy can rid them of all persisting *M. leprae*. The risk of reinfection is likely to be most prominent in areas where leprosy is endemic. It appears important to measure the frequency with which lepromatous patients "relapse" once they have attained smear negative status.

The objectives of this study were: 1) to determine the frequency with which *M. leprae* reappear in skin smears among smear negative lepromatous (LL) and borderline lepromatous (BL) patients on dapsone monotherapy, and 2) to determine whether the duration of smear negative status in such patients influences the risk of *M. leprae* reappearing in skin smears.

Gudiyatham Taluk is the leprosy control area of the Schieffelin Leprosy Research and Training Centre, Karigiri. The prevalence of leprosy in the area has been over 15 per 1000, and about a fifth of all registered patients are clinically diagnosed to have LL or BL leprosy. Fairly accurate records are available of the treatment and progress of each patient from the start of treatment. DDS monotherapy was widely used until 1981, and DDS tablets were delivered to the patients at village clinics for domiciliary treatment. Intensive case detection is effected by repeated house-to-house surveys and health education. A well-equipped base hospital supports the program.

PATIENTS AND METHODS

All known LL and BL patients resident in Gudiyatham Taluk were enumerated from the village clinic register maintained by the institution. Data on these patients were compiled from the individual records of each patient. Smears had been taken from four routine sites (earlobe and chin on the right side, forehead and buttock/thigh on the left side) as well as apparently active sites, generally at one-year intervals. Reading of smears was done by trained personnel at the base hospital, who were given no information about the patient. Techniques and criteria for smears remained unchanged throughout the period under study.

The period of smear negativity in a patient is defined as the single longest period during which the patient was continuously smear negative while under treatment. The sum of the periods of smear negativity for a group of patients yields the "person-years" of smear negativity for that group of patients. "Relapse" is taken to mean the reappearance of *M. leprae* in skin smears after smear negativity. This could be due to reinfection from other patients, or to the patient's own persisting organisms, or both.

RESULTS

A total of 1580 LL and BL patients were on the treatment register on 31 December 1977. Information was available from the start of treatment in each patient up to 28 February 1981 for 1423 (90%) of these patients. Of those 1423 patients 131 had re-

[1] Received for publication on 8 March 1983; accepted for publication in revised form on 25 April 1983.

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THE TABLE. *Annual "relapse" rate by period of smear negativity among LL and BL patients on DDS monotherapy.*

Period of smear negativity (yrs)	No. patients observed	No. person-years of smear negativity	No. patients with "relapse"	Annual "relapse" rate (%/yr)
Initial 2	1293	2494	70	2.8%
>2	1106	8299	92	1.1%
>8	620	2945	26	0.9%

mained continuously smear positive up to 28 February 1981. The 1293 (90.9%) out of the 1423 patients who had at some time been smear negative are included in the analysis.

Of the 1293 patients, 1106 had been smear negative for >2 years. These 1106 patients had 8299 person-years of smear negativity from the third year onwards, with 92 "relapses"; yielding an annual relapse rate of 1.1% per year in this group. Similarly, 620 of the 1293 patients had been smear negative for >8 years. These 620 patients had 2945 person-years of smear negativity from the ninth year onwards, with 26 relapses; the annual relapse rate in this group is thus 0.9% per year.

In contrast, during the initial two years of smear negativity, the 1293 patients had a total of 2494 person-years of smear negativity with 70 relapses; a relapse rate of 2.8% per year. The Table lists the relapse rates in these different groups of patients.

Of the 1293 patients, 694 (53.7%) had collected ≥80% of their prescribed DDS tablets during the period in which they had had negative smears. Six hundred six (606) of these 694 patients had been smear negative for >2 years. These 606 patients had 4553 person-years of negativity from the third year onwards with 31 relapses, yielding an annual relapse rate of 0.7% per year.

DISCUSSION

The "relapse" rate for smear negative LL and BL patients on DDS monotherapy is found to show a progressive decrease as the duration after the attainment of smear negativity increases. During the first two years of smear negativity, the relapse rate is 2.8% per year. From the third year onwards, the "relapse" rate is only 1.1% per year, and by the eighth year it has fallen to 0.9% per year. This means that if 100 LL and BL patients who have been smear negative for two years are observed for a further period while on DDS monotherapy, only one of them on the average is found to "relapse" each year. Further, among smear negative LL and BL patients who collect ≥80% of their prescribed DDS tablets, the relapse rate from the third year of smear negativity onwards is only 0.7% per year. Over half of the smear negative LL and BL patients were found to collect ≥80% of their tablets.

The low rates of relapse found in this study are in keeping with a previous report by Noordeen ([1]) on 125 South Indian lepromatous patients on DDS monotherapy. The suggestion made in that paper that "probably 6 years of treatment, after a case of lepromatous leprosy becomes smear negative, may be adequate," deserves consideration. Over half of the lepromatous patients on DDS monotherapy in Gudiyatham Taluk were found to have been smear negative for more than six years. Noordeen pointed out that after six years of smear negativity, the risk of relapse "was not affected by whether the patients took treatment regularly or irregularly" ([1]). Therefore, cessation of DDS monotherapy after six years of smear negativity may not increase the risk of relapse in a patient. Concurrent comparison of relapses following limited periods of either DDS monotherapy or combination drug therapy in smear negative LL and BL patients should yield valuable information.

SUMMARY

At the Schieffelin Leprosy Research and Training Centre, Karigiri, India, an analysis of "relapse" rates was undertaken on all the 1293 residents of Guidyatham Taluk who were known to have lepromatous (LL) or borderline lepromatous (BL) leprosy and had attained "smear negative" status. "Relapse" was defined as the reappearance of acid-fast bacilli (AFB) in skin smears, whether by reinfection from other patients or from the patient's own persisting organisms. The "relapse" rate decreased steadily with the time elapsed after the attainment of smear negativity: 2.8% (2.8 per 100 patients per year) in the initial two years; 1.1%

from the third year onwards; and 0.9% from the ninth year onwards. Of the 1293 patients, 694 (53.7%) had taken ≥80% regular dapsone (DDS) treatment during smear negativity. In this group, the "relapse" rate from the third year onwards was only 0.7% per year.

The vast majority (90.9%) of LL and BL patients on DDS monotherapy in the area had at some point attained smear negative status. It appears important to study whether a limited period of DDS monotherapy after the attainment of negative skin smears would be an effective alternative to life-long DDS treatment in LL and BL patients.

RESUMEN

En el Centro Schieffelin de Investigación y Adiestramiento de la Lepra, Karigiri, India, se hizo un estudio sobre el grado de recaídas en 1293 residentes de Gudiyatham Taluk que habían tenido lepra lepromatosa (LL) o intermedia (BL) y que habían alcanzado el estado de negativos según los resultados de las preparaciones de linfa cutánea. La "recaída" se definió como la reaparición de bacilos ácido resistentes (BAAR) en las preparaciones de linfa cutánea por reinfección a partir de otros pacientes o de los microorganismos persistentes en el propio paciente. El grado de "recaídas" disminuyó sostenidamente con el tiempo transcurrido después de alcanzar la negatividad en las preparaciones de linfa cutánea: 2.8% (por año) en los dos años iniciales; 1.1% del tercer año en adelante, y 0.9% después del noveno año. De los 1293 pacientes, 694 (53.7%) habían seguido un tratamiento con una regularidad del 80% o mayor a base de DDS y en este grupo, el grado de recaídas del tercer año en adelante fué sólo del 0.7% por año.

La gran mayoría (90.0%) de los pacientes LL y BL bajo tratamiento solo con DDS alcanzaron en algún momento el estado de negativos según las preparaciones de linfa cutánea. Parece importante estudiar si un período limitado de monoterapia con DDS después de alcanzar la negatividad en las preparaciones de linfa cutánea, podría ser una alternativa al tratamiento de por vida con DDS en los pacientes LL y BL.

RÉSUMÉ

Au Schieffelin Leprosy Research and Training Centre, de Karigiri, en Inde méridionale, on a procédé à l'analyse des taux de récidive dans l'ensemble des 1293 résidents du Guidyatham Taluk connus pour être atteints de lèpre lépromateuse (LL) ou dimorphe lépromateuse (BL), ayant atteint le stade de négativation bactériologique dans les frottis. Une "récidive" a été définie comme la réapparition de bacilles acido-résistants dans des frottis cutanés, soit à la suite de réinfection à partir d'autres malades, ou par réinfection endogène par des organismes persistant chez le même malade. Le taux de récidive a décru régulièrement avec le temps, après qu'un état de négativité bactériologique ait été obtenu. Ce taux était de 2.8% (2.8 pour 100 malades par an), au cours des deux premières années; 1.1% à partir de la troisième année et ensuite; de 0.9% à partir de la neuvième année. Parmi les 1293 malades, 694 (53.7%) avaient continué à suivre un traitement régulier par la dapsone (DDS), à raison de ≥80% de la dose prescrite, au cours de la période de négativité des frottis. Dans ce groupe, le taux de récidive à partir de la première année et au-delà n'a été que de 0.7% par an.

La grande majorité (90.9%) des malades LL et BL, soumis à la monothérapie par la DDS, dans cette région, a, à un moment ou l'autre, présenté des frottis négatifs. Il apparaît important d'étudier si une période limitée de monothérapie par la DDS, après que les frottis cutanés soient devenus négatifs, pourrait constituer un moyen efficace de substitution au traitement à la DDS prolongé pour toute la vie, chez les malades LL et BL.

Acknowledgments. We thank the staff of the departments of Epidemiology and Leprosy Control, and Laboratories; particularly Mr. J. Samuel. Mr. Raja Rao typed the manuscript.

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