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Characteristics of patients in the THELEP trials of chemotherapy of leprosy at Bamako and Chingleput

Subcommittee on Clinical Trials of the Chemotherapy of Leprosy (THELEP) Scientific Working Group of the UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases

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Summary The characteristics evident before beginning treatment of 215 lepromatous patients admitted to the THELEP clinical trials of combined chemotherapy at Bamako and Chingleput, including age, sex, BI, LIB, $\log_{10}$ of the number of acid-fast bacilli per gramme tissue, clinical classification, and histopathological classification, have, in general, been found to be uniformly distributed between treatment centres, and among the regimens within each centre. Thus, there appears little likelihood that the results of treatment by the trial regimens will have been influenced by any of these characteristics. Except for the clinical and histopathological classifications, which did not agree more frequently than predicted by chance, the expected interrelationships among these characteristics were demonstrated.

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Introduction

During the latter half of 1978, admission of patients was begun into controlled clinical trials of combined chemotherapy among previously untreated patients with lepromatous leprosy at Bamako, Mali, and Chingleput, South India. The last patients were recruited during the latter half of 1983, by which time 99 patients had been admitted to the trial in Bamako and 116 into that at Chingleput. The patients were randomized among 5 regimens,* which were to be

* Patients were allocated among 6 treatment groups, 3 in each centre; however, 1 of the 5 regimens (regimen C) was employed in both centres.

Bamako regimens:

A_2, rifampicin, protionamide and dapsone, each in a daily dose of 600, 500, and 100 mg, respectively, for 2 years;

C, rifampicin, in a single initial dose of 1500 mg, and dapsone, 100 mg daily for 2 years;

E_2, rifampicin, 900 mg once weekly, and protionamide, 500 mg daily for the first 3 months, together with dapsone, 100 mg daily for 2 years.

Chingleput regimens:

A_1, rifampicin, clofazimine and dapsone, each in a daily dose of 600, 100, and 100 mg, respectively, for 2 years;

C, as for Bamako;

D_1, rifampicin, in a single initial dose of 1500 mg, clofazimine, in a daily dose of 100 mg for the first 3 months, and dapsone, 100 mg daily for 2 years.[1]

compared in terms of effectiveness in reducing the numbers of detectable persisting *Mycobacterium leprae* in skin-biopsy specimens obtained from the patients at intervals during the trials.[1] Intensive study of the 215 patients with previously untreated lepromatous leprosy has yielded considerable information with respect to the characteristics of the patients observed before treatment was instituted. The purpose of this paper is to analyse the distributions of these characteristics among the trial regimens, and to study interrelationships among the pretreatment characteristics.

Materials and methods

The patients recruited into the two trials and the methods employed in the trials are those already described.[1] In brief, patients with LL, LI or BL* leprosy were recruited who denied prior treatment, and in whose urine dapsone and its metabolites were not detectable. At each trial centre, before treatment was begun, the patients' disease was classified clinically, multiple smears of slit skin-scrapings were examined for measurement of the bacteriological index (BI), and skin-biopsy specimens were obtained and air-shipped to the UK. The fresh specimens were weighed, the numbers of *M. leprae* counted, and the susceptibility of the organisms to dapsone measured in the Department of Medical Microbiology, St George's Hospital Medical School, London. Histopathological examination, including Ridley–Jopling classification[2] and measurement of the logarithmic biopsy index (LIB),[3] were performed on the fixed specimen in the Department of Dermatology, The Slade Hospital, Oxford.

Data were analysed by means of a number of statistical techniques, including: 1, the X^2 and Fisher exact probability techniques for comparison of frequencies among two or more categories, e.g. the various clinical classes; 2, the Mann–Whitney *U* test and the Kruskal–Wallis one-way analysis of variance, for comparison of two or more groups of data, e.g. the distribution of patient-age between centres and among regimens; 3, the product–moment correlation coefficient, for analysis of the relationships between two continuous variables, e.g. BI and LIB; and 4, Kappa, for analysis of the degree of correspondence between 2 systems of classification, e.g. CLINCLAS and HISTCLAS.[4–7]

Results

Age and sex

The distribution by age and sex of the patients admitted into the two trials is

* The Ridley–Jopling system of classification of leprosy, a system based on clinical, histopathological and other criteria, employs the following terminology: BL, borderline-lepromatous; LI (or LL_s), sub-polar lepromatous leprosy; LL (or LL_p), polar lepromatous leprosy.[2]

Table 1. Distribution of patients by age and sex.

	Bamako regimen				Chingleput regimen			
	A_2	C	E_2	All	A_1	C	D_1	All
Number of patients	12	44	43	99	39	39	38	116
Median age	26	26	25	25	29	30	25·5	29
Number of males	12	44	43	99	36	36	33	105

Patient-age did not differ significantly between centres ($P=0·08$) or among regimens within centres (for Bamako, $P=0·65$; for Chingleput, $P=0·70$). The proportions of male and female patients did not differ significantly among Chingleput regimens ($P>0·10$).

shown in Table 1. The median age may be seen to be 30 or less for all regimens in both treatment centres. No significant difference of age was found between the two centres, nor among the regimens within each centre. It is evident from the data of Table 1 that only male patients were recruited in Bamako, and only a few female patients were recruited in Chingleput; in the latter centre, the proportion of female patients did not differ significantly among the 3 regimens.

Pretreatment BI, LIB and logarithm$_{10}$ of the number of acid-fast bacilli (AFB) per gramme

Median initial values of the BI, LIB and logarithm$_{10}$ of the number of AFB per g of biopsy specimen (LAFBPG) are shown for each regimen and each centre in Table 2. The median BI lay between 4 and 5 on Ridley's logarithmic scale,[8] the median LIB between 5 and 6, and the median value of the LAFBPG between 8·3 and 8·5 (the median numbers of AFB in the pretreatment biopsy specimen lay in the range 200–300 million) for all regimens in both centres. The BI was significantly larger among Bamako than among Chingleput patients, and the LIB was significantly larger among the latter. No significant difference of the LAFBPG was found between the centres, nor of the pretreatment values for BI, LIB and LAFBPG among regimens within the centres. As expected, the individual initial values for BI, LIB, and LAFBPG were closely interrelated (see Table 3).

Clinical and histopathological classifications

The distribution of patients between treatment centres and among regimens according to clinical classification (CLINCLAS) is shown in Table 4. In both centres, the majority of patients (75% in Bamako; 69% in Chingleput) were

Table 2. Distribution of patients by initial BI, LIB and LAFBPG.

	Bamako regimen				Chingleput regimen			
	A_2	C	E_2	All	A_1	C	D_1	All
Number of patients	12	41	38	91	39	39	38	116
Median BI	4·75	4·50	4·50	4·67	4·33	4·17	4·42	4·33
Number of patients	12	44	43	99	39	39	38	116
Median LIB	5·5	5·3	5·0	5·3	5·6	5·5	5·5	5·5
Number of patients	12	42	41	95	39	37	35	111
Median LAFBPG	8·3	8·5	8·4	8·4	8·5	8·3	8·4	8·4

The BIs of Bamako patients were significantly larger than those of Chingleput patients ($P=0·003$), but no significant differences of the BI among regimens within centres were discerned (for Bamako, $P=0·23$; for Chingleput, $P=0·16$). The LIB is significantly larger among Chingleput than among Bamako patients ($P=0·01$), but no significant differences were observed among regimens within centres ($P=0·09$). No significant differences of LAFBPG were found between centres ($P=0·96$) or among regimens within centres ($P=0·54$).

Table 3. Interrelationships among the pretreatment values for BI, LIB and LAFBPG.

Interaction	(Product-moment correlation coefficient) (Probability)		
BI × LIB	0·58 / 0·0001	0·32 / 0·0005	0·44 / 0·0001
BI × LAFBPG	0·49 / 0·0001	0·49 / 0·0001	0·49 / 0·0001
LIB × LAFBPG	0·65 / 0·0001	0·38 / 0·0001	0·53 / 0·0001

Table 4. Distribution of patients by initial CLINCLAS.

	Number of patients							
	Bamako regimen				Chingleput regimen			
CLINCLAS	A_2	C	E_2	All	A_1	C	D_1	All
LL	0	7	7	14	11	8	8	27
LI	12	32	30	74	25	26	29	80
BL	0	5	6	11	3	5	1	9

The proportion of patients classified LL did not differ significantly between centres nor among regimens (for Bamako, $X^2 = 2{\cdot}26$, $P > 0{\cdot}10$; for Chingleput, $X^2 = 0{\cdot}79$, $P > 0{\cdot}90$).

Table 5. Distribution of patients by initial HISTCLAS.

	Number of patients							
	Bamako regimen				Chingleput regimen			
HISTCLAS	A_2	C	E_2	All	A_1	C	D_1	All
LL	1	1	0	2	0	1	0	1
LI	11	37	31	79	38	37	36	111
BL	0	5	9	14	0	1	2	3
Other	0	1	3	4	1	0	0	1

The proportion of patients classified BL or 'other' is significantly higher among Bamako than among Chingleput patients ($X^2 = 10{\cdot}1$; $P < 0{\cdot}01$). No significant difference of the proportion classified BL or 'other' was found among regimens within centres (for Bamako, $P = 0{\cdot}07$; for Chingleput, $P = 0{\cdot}77$).

classified LI, and the proportions of patients classified LL, LI or BL did not differ significantly between centres or among regimens within each centre. The majority of patients in both centres (80% in Bamako; 96% in Chingleput) were LI by histopathological classification (HISTCLAS), as shown in Table 5. Although the proportion of patients classified BL or 'other' did not vary significantly among regimens within each centre, the proportion of patients with HISTCLAS BL or other was significantly greater in Bamako (14%) than in Chingleput (3%). It must

Table 6. Agreement of CLINCLAS with HISTCLAS.

	Number of patients					
	Bamako: CLINCLAS			Chingleput: CLINCLAS		
HISTCLAS	LL	LI	BL	LL	LI	BL
LL	0	2	0	0	1	0
LI	13	60	6	26	76	9
BL	1	10	3	1	2	0
Other	0	2	2	0	1	0

The agreement of CLINCLAS with HISTCLAS is not much different from that expected by chance (Kappa for Bamako = −0·05; for Chingleput = 0·30).

be noted, however, that statistical analysis of the data on HISTCLAS in Tables 5 and 6 are complicated by the presence of many categories including fewer than 5 patients.

The correlation between CLINCLAS and HISTCLAS, described in Table 6, shows agreement of 64% in Bamako and 66% in Chingleput. Table 6 also reveals that LI leprosy was clinically under-diagnosed in both centres. Fourteen per cent of Bamako patients and 22% of Chingleput patients were LL by CLINCLAS, but LI or BL by HISTCLAS; and 6% of Bamako patients and 8% of Chingleput patients were BL by CLINCLAS, but LI by HISTCLAS. Because both classifications include very large proportions of LI patients, i.e. 190 of 215 (88%) LI by HISTCLAS, and 154 of 215 (72%) LI by CLINCLAS, one expects that, by chance, 63% ($0{\cdot}88 \times 0{\cdot}72$) of the patients would be considered LI by both CLINCLAS and HISTCLAS. In fact, this is what was found. That the value of Kappa is smaller than 0·4 for both centres appears to confirm the poor agreement between the two methods of classification. Kappa, the statistic employed to examine the degree of agreement between two classifications,[7] measures the excess of agreement over that resulting from chance; however, this statistic is sensitive to skewed distributions, such as those encountered here, so that this result must be interpreted cautiously.

Neither the LIB nor the LAFBPG was found to vary significantly with CLINCLAS in either centre, whereas, for Bamako patients, the mean BI was significantly smaller for patients with CLINCLAS BL than for patients with CLINCLAS LL or LI (see Table 7). The relationships between BI, LIB and LAFBPG, and HISTCLAS could not be analysed in the same way, because so many of the categories included fewer than 5 patients.

Table 7. Relationships among the pretreatment values for BI, LIB and LAFBPG, and CLINCLAS.

	Bamako: CLINCLAS			Chingleput: CLINCLAS		
	LL	LI	BL	LL	LI	BL
Median BI	4·7	4·7	3·7	4·3	4·3	4·3
Median LIB	5·6	5·3	5·0	5·5	5·6	5·6
Median LAFBPG	8·6	8·4	8·3	8·3	8·4	8·2

No significant differences among values of the BI, LIB or LAFBPG were found for the several clinical classes.

Discussion

Before embarking upon an analysis of the results of a clinical trial of treatment regimens to which patients were assigned by random allocation, it is necessary to ensure that the trial has not been biased by the assignment to one regimen of a disproportionately large number of patients possessing a characteristic that might have influenced the results of treatment. In fact, analysis of two clinical trials among previously untreated patients with lepromatous leprosy conducted in Cebu (one a comparison of several regimens of clofazimine, and the other a comparison of rifampicin with dapsone, both as monotherapy) suggested an influence upon the rate of response, as measured in mice, of the $\log_{10}$ number of AFB (LAFB) in the patients' pretreatment biopsy-specimens,[9] however, as a result of the random allocation of patients to regimen, a disproportionately large number of patients with large or small values of the LAFB was not assigned to one of the regimens. Of course, one can examine the distribution across regimens of only those characteristics of patients that were identified before the trial was begun, and for which the patients were specifically examined and the results of the examinations recorded. There remains the possibility that the trial might be biased because of the maldistribution of some important patient characteristic that had not been identified.

It is, therefore, reassuring to note that, in the THELEP trials, the patient-characteristics that had been identified were not maldistributed. As reported elsewhere,[10] patients found to harbour dapsone-resistant *M. leprae* before treatment, and those whose organisms, recovered from pretreatment biopsy specimens, could not be tested for susceptibility to dapsone, were not maldistributed between centres nor among regimens within centre. And as shown here, random allocation of patients to regimen resulted in a distribution of patients according to age, pretreatment BI, LIB and LAFBPG, CLINCLAS and

HISTCLAS that, with only three exceptions, did not differ significantly between treatment centres nor among regimens within centre. These exceptions were the pretreatment BI, which was larger among Bamako than among Chingleput patients, the pretreatment LIB, which was larger among Chingleput than among Bamako patients, and a greater proportion of patients with HISTCLAS BL or 'other' among Bamako than among Chingleput patients. Because both of the latter two measurements were performed in Oxford on specimens from both centres,[1] these differences between the two centres. On the other hand, measurements of the BI were performed at each centre.[1] Although smear-reading at both centres was evaluated on a continuing basis at the Center for Infectious Diseases, Centers for Disease Control, Atlanta, Georgia, USA, it is possible that the technique of the measurement differed between Bamako and Chingleput. In no case, however, was the characteristic maldistributed among regimens within centre. Therefore, in analysing the results of these trials, one may confidently compare the regimens within each centre, and the results may be compared between centres with almost equal confidence.

A second purpose for an analysis of the pretreatment characteristics of the patients is to exploit the opportunity provided by the careful study of a relatively large number of patients, all at the same stage of treatment, to examine interrelationships among these characteristics. As expected, the measures of bacterial load—BI, LIB and LAFBPG—were all significantly intercorrelated. On the other hand, as indicated by the product-moment correlation coefficients, which range between 0·32 and 0·65, the correlations were by no means perfect.

One might also have expected close correspondence between CLINCLAS and HISTCLAS. However, this was not found in these trials, the agreement between these two measures being only 64 and 66% in Bamako and Chingleput, respectively. One possible explanation for this less-than-complete agreement is a systematic difference between the interpretation of clinical criteria at the two treatment centres and that of the histopathological criteria in Oxford. In neither centre had classification previously employed the LI class, nor had there been an earlier opportunity for the clinicians to adjust their diagnostic criteria to the results of histopathological examination. There are no data upon which to judge the degree of correspondence in clinical diagnosis between centres. On the other hand, because these problems were foreseen in the design of the trials, attempts were made, by the efforts of a coordinator experienced in clinical trials, by a workshop held at one of the centres before beginning the trials, in which responsible clinicians from both centres participated, and by the participation of the coordinator and clinicians from both centres in meetings of the THELEP Subcommittee on Clinical Trials, to achieve a common set of diagnostic criteria. An alternative explanation for the lack of agreement between CLINCLAS and HISTCLAS is that clinical classification is based upon examination of many lesions, whereas histopathological classification, as carried out in these trials, was

based upon examination of only one lesion; the lesion selected for repeated biopsy may not have been the most representative of the patient's lesions.

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