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Are 18 Doses of WHO/MDT Sufficient for Multibacillary Leprosy; Results of a Trial in Malawi¹

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A study was initiated in 1987 among multibacillary (MB) patients in Malawi within the framework of the LEPRO Control and Evaluation Projects and the Shire Valley Leprosy Control Project to investigate whether treatment of MB patients can be shortened without increasing the number (percentage) of unfavorable outcomes. Until the beginning of the study, MB patients in Malawi were treated with 100 mg of dapsone and 50 mg of clofazimine daily as well as 600 mg of rifampin and 300 mg of clofazimine supervised monthly, as recommended since 1982 by the World Health Organization (WHO) (¹³). This multidrug treatment (MDT) was given for at least 24 months and continued thereafter until two consecutive slit-skin smears showed bacterial indexes (BIs) of 0 in line with WHO recommendations (¹³). Several countries adopted a policy of only 24 months' treatment even if one or more slit-skin smears were still positive at that time.

In the absence of any definitive long-term study in which MB patients received 24 monthly doses of MDT, we decided to com-

pare different durations of the above described MDT: 18 versus 30 monthly doses (i.e., 6 months shorter versus 6 months longer than the recommended minimum of 24 months).

If long-term outcomes after 18 monthly doses of WHO/MDT are at least as good as long-term outcomes after 30 monthly doses, then such a result would open the way a) to introduce 18-month treatment regimens for MB leprosy and b) to study even shorter WHO/MDT durations for MB leprosy patients. Shorter treatment regimens allow for easier patient compliance and perhaps even more importantly, makes it easier to implement and sustain a national program.

Long-term results have to be measured in terms of relapse rates and incidence rates of disabilities during and after MDT; the latter being the more important since disabilities are the main problem for patients and make leprosy a public health problem. Relapse rates are probably of lesser importance as long as relapses can be treated successfully.

METHODS

For the purpose of this study a MB leprosy patient was defined as a) any untreated leprosy patient with a BI of 2 or higher in a slit-skin smear from any site or b) any untreated patient in whom a skin or nerve

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TABLE 1. Frequency distribution of highest BIs at the time of registration by treatment group.

BI at time of registration	Treatment group			
	18 doses		30 doses	
	No.	%	No.	%
0	12	7.6	9	6.1
1	2	1.3	2	1.4
2	12	7.6	14	9.5
3	21	13.4	25	16.9
4	49	31.2	47	31.8
5	35	22.3	23	15.5
6	26	16.6	28	18.9
Total	157		148	

biopsy yielded evidence of MB leprosy or c) any newly registered relapse with evidence of MB leprosy.

The BI was measured according to the (logarithmic) Ridley scale (⁹). Slit-skin smears were taken from both earlobes and from at least two skin lesions at registration (the beginning of treatment).

We only recruited patients into the study who were born after 1918, lived in an area accessible at least by motorcycle, and after they had received 18 supervised monthly doses of 600 mg rifampin plus 300 mg clofazimine within 24 months of registration. At this point in time patients were randomly allocated to either stop antileprosy treatment or to take a further 12 monthly doses of MDT to make a total of 30 doses (which had to be taken by the patient within 40 months of registration). The method adopted was that the leprosy control assistants (LCAs) looking after the patients opened a sealed envelope with the instruction for either 18 or 30 doses at the time of giving the 18th monthly dose of WHO/MDT. The procedure was closely supervised by senior staff. Overt type 1 reaction and recent deficit in nerve function were treated with steroids as described previously (²). Severe or recurrent type 2 reactions were treated with 300 mg clofazimine daily tapered down to zero over 18 months. Dapsone and rifampin were discontinued in these patients according to their treatment group.

Table 1 shows the frequency distribution of the highest BIs in slit-skin smears at the time of registration by treatment group. The

TABLE 2. Frequency distribution of ages of patients at the time of registration by treatment group.

Age group at time of registration	Treatment group			
	18 doses		30 doses	
	No.	%	No.	%
0-14	2	1.3	8	5.4
15-29	38	24.2	25	16.9
30-44	66	42.0	65	43.9
45-59	32	20.4	42	28.4
60-	19	12.1	8	5.4
Total	157		148	

mean BI in the 18-dose group was 3.92; the mean BI in the 30-dose group was 3.89. The highest BI was < 2 in 25 of the 305 patients recruited into the study. In these patients there was histopathological evidence of MB leprosy (see b above). Of the 305 patients, 259 (84.9%) were new untreated cases, 133/157 in the 18-dose group and 126/148 in the 30-dose group.

At the time of randomization 75 (47.8%) patients allocated to stop treatment had a BI of 0; the corresponding figure for patients allocated to a further 12 doses of WHO/MDT was 68 (45.9%).

The age distribution of patients at the time of registration by treatment group is shown in Table 2. Nearly half the patients in each group were 30 to 44 years old. In each treatment group a third of the patients were female.

For the grading of disabilities, we used the 1960 WHO classification (¹²); grade 1 = anesthesia of hands and/or feet, grade 5 = extensive loss of fingers and/or loss of more than one third of a foot and/or blindness due to leprosy. The term marked disability as used for the outcome with respect to disabilities implies at least one of the following: lagophthalmos, paralysis or loss of a finger, a plantar ulcer or a foot drop. At the time of registration 124 (79.0%) patients in the 18-dose group and 114 (77.0%) patients in the 30-dose group had no disabilities although some of them had anesthesia (Table 3).

After randomization patients were reviewed by LCAs every 6 months, usually at their homes. At each review a full clinical examination was carried out and slit-skin

TABLE 3. Frequency distribution of highest disability grades among patients at the time of registration by treatment group.

Disability grade (WHO 1960)	Treatment group			
	18 doses		30 doses	
	No.	%	No.	%
0	104	66.2	97	65.5
1	20	12.7	17	11.5
2	14	8.9	17	11.5
3	11	7.0	8	5.4
4	8	5.1	8	5.4
5	0		1	0.7
Total	157		148	

smears were taken from the same sites as at registration. Smears were examined by laboratory assistants without knowing previous results. The following definition of a relapse was decided upon before the start of the trial: a) MB relapse: if the highest BI of any site shows an increase $\geq 2+$ compared with the highest BI of any site in the previous smears. This new result might be from the smears of an old lesion or from the smear of a new lesion. Such an increase in BI should be accompanied by an increase in the proportion of fragments + solids. The percentage of solids + fragments in the actual smear minus the percentage of solids + fragments in the previous smear should be $\geq 10\%$. b) PB relapse: definite clinical evidence of PB leprosy found by one of the investigators and/or definite histopathological evidence of PB leprosy in a new lesion.

The envisaged follow-up period was 5 years after randomization. The actual dis-

TABLE 4. Frequency distribution of follow-up periods after intake into the study by treatment group.

Length of follow up (mos.)	Treatment group			
	18 doses		30 doses	
	No.	%	No.	%
0	10	6.4	2	1.4
6	16	10.2	1	0.7
12	8	5.1	12	8.1
18	12	7.6	17	11.5
24	12	7.6	13	8.8
30	18	11.5	18	12.2
36	17	10.8	19	12.8
42	20	12.7	17	11.5
48	8	5.1	10	6.8
54	6	3.8	10	6.8
60	12	7.6	7	4.7
66	15	9.6	15	10.1
72	2	1.3	4	2.7
78	1	0.6	3	3.0
Total	157		148	

tribution of follow-up periods is shown in Table 4 and Figure 1. The mean follow-up periods were 33.9 months and 38.2 months for patients allocated to 18 and 30 doses of WHO/MDT respectively.

The human immunodeficiency virus (HIV) status of patients was ascertained only at registration in the area covered by the LEPRO Evaluation Project but results were not used in this analysis (⁸).

Data were entered on computers and tabulated using EPI INFO software.

RESULTS

No relapse was observed in either treatment group.

Table 5 and Figure 2 show conditional and cumulative probabilities of patients remaining slit-skin smear positive after 18 doses of WHO/MDT by treatment group (^{1,3}). At the time of randomization 82 of the 157 patients allocated to 18 doses (M18) and 80 of the 148 patients allocated to 30 doses (M30) still had a highest BI of ≥ 1 . The BI of all patients, as far as the patients remained available for review, fell to 0 by 60 months. From month 6 onward cumulative probabilities of remaining slit-skin smear positive were constantly higher for the M18 group than for the M30 group. The difference is statistically marginally significant (log rank test, $\chi^2 = 4.23$, $p < 0.05$).

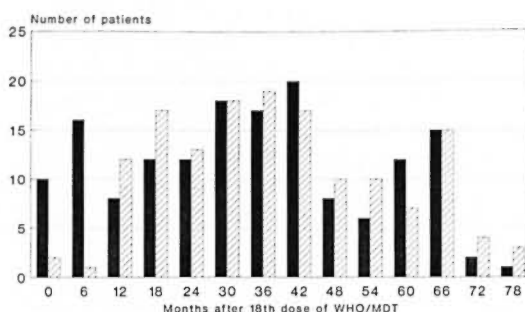


FIG. 1. Frequency distribution of follow-up periods after 18 doses of WHO/MDT by treatment group. ■ = 18-dose group; ▨ = 30-dose group.

TABLE 5. Cumulative probabilities of remaining slit-skin smear positive after 18 doses WHO/MDT by treatment group.

Mo.	n M18	d M18	l M18	n M30	d M30	l M30	p+ M18	p+ M30	c M18	c M30
6	82	19	2	80	16	2	0.765	0.797	0.765	0.797
12	61	5	2	62	14	0	0.917	0.774	0.702	0.617
18	54	8	3	48	12	1	0.848	0.747	0.595	0.461
24	43	14	3	35	11	1	0.663	0.681	0.394	0.314
30	26	4	2	23	10	0	0.840	0.565	0.331	0.178
36	20	5	3	13	4	1	0.730	0.680	0.242	0.121
42	12	4	1	8	5	1	0.652	0.333	0.158	0.04
48	7	2	2	2	1	0	0.667	0.5	0.105	0.02
54	3	2	0	1	0	1	0.333	0	0.035	0.02
60	1	1	0	0			0		0	

n = number of patients slit-skin smear positive at beginning of follow-up period.

d = number of patients whose BI became 0 during the period.

l = number of patients lost (censored) during the period.

p+ = conditional probability of remaining slit-skin smear positive.

c = cumulative probability of remaining slit-skin smear positive.

M18 = 18-dose treatment group.

M30 = 30-dose treatment group.

Among the patients allocated to 18 doses, 61 (38.9%) were found either with a recent deficit in nerve function or developed at least one overt type 1 reaction; among those allocated to 30 doses the number was 48 (32.4%). Table 6 shows that the vast majority of type 1 reactions occurred before randomization and that considerably more were observed in the M18 than in the M30 group.

The results of review examinations with respect to disabilities are shown in Table 7. Of the 157 patients allocated to 18 doses of WHO/MDT, 86 (54.8%) never had any disability; of the 148 patients allocated to 30 doses, the number was 87 (58.8%). Altogether 50 patients developed minor or marked new disabilities, 30 (19.1%) in the

M18 group, 20 (13.5%) in the M30 group. The difference is statistically not significant (Mantel-Hänsel, $p = 0.19$). Another 18 and 12 patients, respectively, experienced a worsening of their disabilities in the two treatment groups. If these are combined with those patients who developed new disabilities, the difference between the two treatment groups approaches statistical significance ($p = 0.076$).

The relationship between episodes leading to treatment with steroids (either because of recent nerve damage or because of overt type 1 reactions) and the outcome with respect to disabilities is also shown in Table 7. There is a highly significant relationship between the two ($p = 0.006$). For example, 17 (9 + 8) of 109 patients (15.6%) with a type 1 reaction developed new disabilities, while only 11 (6 + 5) of 196 patients (5.7%) who did not have a reaction suffered new disabilities. This underlines the fact that type

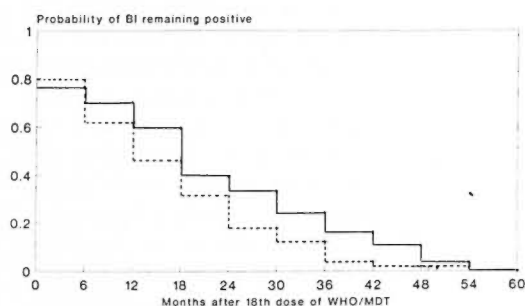


FIG. 2. Cumulative probabilities of remaining slit-skin smear positive after 18 doses of WHO/MDT by treatment group. — = 18-dose group; --- = 30-dose group.

TABLE 6. Frequency distribution of type 1 reactions before and after randomization by treatment group.

Period during which type 1 reaction occurred	Treatment group			
	18 doses		30 doses	
	No.	%	No.	%
Before randomization	54	88.5	38	79.2
After randomization	7	11.5	10	20.8
Total	61		48	

TABLE 7. Outcome with respect to disabilities by treatment group and by occurrence of type 1 reaction.

Outcome	Treatment group				No type 1 reaction		Type 1 reaction treatment received at least once	
	18 doses		30 doses					
	No.	%	No.	%	No.	%	No.	%
Never any disabilities	86	54.8	87	58.8	124	63.3	49	45.0
None at registration, but development of marked new disability	10	6.4	5	3.4	6	3.1	9	8.3
None at registration, but development of minor new disability	8	5.1	5	3.4	5	2.6	8	7.3
Disability at registration and development of independent marked new disability	5	3.2	5	3.4	4	2.0	6	5.5
Disability at registration and development of independent minor new disability	7	4.5	5	3.4	7	3.6	5	4.6
Disability at registration and worsening	18	11.5	12	8.1	18	9.2	12	11.0
Disability at registration and no change	11	7.0	12	8.1	18	9.2	5	4.6
Disability at registration but improved	12	7.6	17	11.5	14	8.9	15	10.1
Total	157		148		196		109	

1 reactions are an important risk factor for the development of disabilities and also that the present steroid treatment, even if instituted quickly, is unsatisfactory.

Severe type 2 reactions occurred in only 9 patients; of these 9 patients 5 were in the M18 group, 4 in the M30 group.

DISCUSSION

There have been a number of trials during the last couple of years trying out new and shorter treatment regimens for MB leprosy (4-7, 10). Our trial is different insofar as we only varied the period of administering a generally recommended and widely accepted treatment regimen (WHO/MDT). This seemed of considerable interest to us in particular since the duration of the recommended regimen was not based on the results of a trial. If 30 doses of WHO/MDT had resulted in a better outcome than 18 doses, the wisdom of giving MDT for only 2 years would have been thrown in doubt.

For practical purposes our trial was not double-blind. Mostly we were concerned that placebo and actual drug treatment (WHO/MDT) might get confused by our

field staff. In addition, we were not sure that it would be ethical to ask patients to walk every month to a treatment point in order to receive a placebo. One effect of this procedure was, unfortunately, that a number of patients in the M18 group were lost early on to follow up after randomization. This explains why the average duration of follow up is shorter for this group (Table 4).

Allocation was randomized as described, and we have shown that randomization was largely successful: patients in the two treatment groups were comparable with regard to age, sex, BIs at registration, and the frequency distribution of disabilities at registration. Only with regard to the occurrence of type 1 reactions did our groups differ in that more type 1 reactions were observed before randomization in the M18 group. Given the relationship between type 1 reaction and the development of new disabilities, this imbalance needs to be discussed further.

Although a number of patients in the trial must have been HIV positive, no relapse was observed in either treatment group. This in contrast to the experience in Mali (5) where

2.9% of a small number of patients developed a relapse during years 3 and 4 of follow up after completion of 24 doses of WHO/MDT. Our results indicate that 18 doses of WHO/MDT may be sufficient concerning relapses. They also show the superiority of WHO/MDT over dapsone monotherapy with regard to relapses (¹¹). On the other hand it still can be argued that a late relapse rate might be higher among patients treated with 18 doses of WHO/MDT than among those treated with 30 doses. This only time will tell.

We have also shown that even without further antileprosy treatment BIs still positive at the time of randomization became 0 in due course. We did, however, observe an interesting difference in the cumulative probabilities of remaining slit-skin smear positive in that patients in the M18 group had a significantly higher cumulative probability of remaining slit-skin smear positive than patients in the M30 group. This argues against reducing the number of doses of WHO/MDT below 18 without a trial.

We further observed that more patients in the M18 group developed disabilities than did patients in the M30 group. While this is most disturbing at first sight, the difference has to be seen in light of the already mentioned fact that more type 1 reactions occurred in patients allocated to the M18 group. However, because the vast majority occurred before randomization (Table 6) this imbalance can only be due to chance. Thus, even the outcome with respect to disabilities is essentially the same in the two groups. This, again, argues in favor of 18 doses of WHO/MDT being sufficient. On the other hand, the overall outcome of antileprosy treatment of MB patients leaves a lot to be desired. As can be seen from Table 7, the percentage of patients who suffered worsening of disabilities (30/305; 9.8%) or new disabilities (50/305; 16.4%) continues to be disturbingly high. The ultimate treatment for MB leprosy has surely not been found yet, and we propose that consideration should be given to the feasibility of a trial in which antiinflammatory drugs are included routinely in the antileprosy treatment for the first 12 to 18 months after registration, during which time most type 1 reactions occur.

Finally, we would like to mention the small number of type 2 reactions observed by us. Presumably this is due to the clofazimine component of WHO/MDT.

SUMMARY

A trial comparing 18 monthly and 30 monthly doses of the World Health Organization-recommended multidrug therapy (WHO/MDT) in 305 multibacillary leprosy patients in Malawi is described. Patients were randomly allocated to one of the two regimens at the time of taking the 18th supervised dose of WHO/MDT. The mean follow-up period was 3 years (maximum 6 years). No relapse was observed in either group. The cumulative probabilities of remaining slit-skin smear positive were significantly higher among patients receiving only the 18 monthly doses of WHO/MDT, but reached zero at month 60 of follow up. The percentage of patients who developed new disabilities during the trial period was similar in both groups. However, the overall percentage of patients who developed new disabilities (50/305, 16.4%) remains disturbingly high. On the whole, the results of the trial argue in favor of 18 monthly doses of WHO/MDT taken within 24 months as being sufficient for the treatment of multibacillary leprosy.

RESUMEN

Se hizo un estudio en 305 pacientes con lepra de Malawi, comparando la efectividad de 18 y 30 dosis mensuales de la poliquimioterapia (PQT) recomendada por la Organización Mundial de la Salud (OMS). Los pacientes se repartieron al azar en cada uno de los dos esquemas de tratamiento, cuando ya habían recibido 18 dosis de la PQT/OMS. El periodo promedio de seguimiento fue de 3 años (máximo de 6 años). En ningún grupo se observaron recaídas. Las probabilidades acumulativas de permanecer positivos en las extensiones de linfa cutánea fueron significativamente mayores entre los pacientes que recibieron sólo las 18 dosis de la PQT/OMS, pero fueron de cero hacia el mes 60 de seguimiento. El porcentaje de pacientes que desarrollaron nuevas alteraciones incapacitantes durante el periodo que duró el ensayo fue similar en ambos grupos. Sin embargo, el porcentaje global de pacientes que desarrollaron nuevas alteraciones incapacitantes (50/305, 16.4%) permaneció preocupantemente alto. De manera general, los resultados del estudio están en favor de las 18 dosis mensuales de la PQT/OMS, tomadas dentro de un periodo de 24 meses,

como suficientes para el tratamiento de la lepra multibacilar.

RÉSUMÉ

On décrit un essai comparatif de 18 et 30 doses mensuelles de la polychimiothérapie aux doses recommandées par l'Organisation Mondiale de la Santé (PCT/OMS). Les patients ont été répartis au hasard pour recevoir l'un ou l'autre des deux régimes thérapeutiques au moment de recevoir leur dix-septième dose de PCT/OMS. La période moyenne de suivi a été de 3 ans (maximum 6 ans). Aucune rechute n'a été observée dans aucun des deux groupes. Les probabilités cumulées de rester positif aux frottis cutanés étaient significativement plus élevées pour les patients qui ont reçu seulement 18 doses mensuelles de PCT/OMS, mais ont atteint zéro au soixantième mois du suivi. Le pourcentage de patients qui ont développé de nouvelles incapacités durant la période d'essai était semblable dans les deux groupes. Cependant, le pourcentage total des patients qui ont développé de nouvelles incapacités (50/305, 16,4%) reste élevé de manière troublante. Dans l'ensemble, les résultats de l'essai plaident en faveur du fait que les 18 doses mensuelles de PCT/OMS prises dans un intervalle de temps de 24 mois seraient suffisantes pour le traitement de la lèpre multibacillaire.

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