A controlled therapeutic trial in paucibacillary leprosy comparing a single dose of rifampicin followed by 1 year of daily dapsone with 10 weekly doses of rifampicin

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Summary Results of prospective therapeutic trials among paucibacillary leprosy patients conducted in 1980–82 in Anjouan, Burundi, Rwanda and Zaire are presented. Regimens were (TrA) rifampicin (RMP) 1500 mg single dose, supervised, followed by 1 year of dapsone 100 mg daily unsupervised; (TrB) RMP 900 mg once a week during 10 weeks and (B-com) RMP 600 mg once a week during 10 weeks.

Regimens are evaluated in terms of cure rates and relapse rates based on the histopathology of skin biopsies.

Among patients with less than 3 skin lesions TrA and TrB perform equally well (96–97% cure rate), in patients with 3 or more skin lesions TrB is superior (98% cure) to TrA regimen (89% cure). Treatment B-com is as effective as TrB. The importance of late cures is stressed.

Relapse rates are comparable in all regimens with a mean of 2.84 per 100 patient years.

Introduction

The treatment of paucibacillary leprosy is important for several reasons. Although multibacillary (MB) leprosy patients constitute undoubtedly the prime source of contagion with *Mycobacterium leprae*, paucibacillary (PB) patients, representing the majority of leprosy cases in most endemic areas, may contribute substantially to the total transmission pressure because of their numerical superiority.^{1,2} Therefore a rapidly bactericidal therapy for PB patients is epidemiologically

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important. Furthermore, in spite of reported spontaneous self-healing of PB leprosy,³ untreated patients may develop neuritis with ensuing complications and invalidities, while others will downgrade to more contagious MB forms.

When only the essentially bacteriostatic drug dapsone (DDS) was available, treatment of PB leprosy was continued for several years. This prolonged therapy resulted in low patient compliance, leading to treatment failures and relapses.^{4,5} The administration of the highly bactericidal drug rifampicin (RMP) should shorten considerably the duration of therapy, and facilitate the integration of leprosy control into the primary health care system.⁶

Because the maximum number of *M. leprae* in PB patients is estimated to be 10⁶ organisms,⁷ which is below the threshold for the appearance of drug-resistant mutants, monotherapy of PB leprosy is justifiable.⁶

Since 1980, PB patients in Zaire, Rwanda, Burundi and on the island of Anjouan (République Fédérale Islamique des Comores) were taken into 'prospective controlled therapeutic trials with regimens containing RMP in monotherapy, or a combination of RMP with DDS.

The present analysis concerns all patients who were taken in from 1980 to 1982.

Patients and methods

Leprosy patients were diagnosed either after self-reporting, or through referral or examination of contacts. All patients were examined clinically and neurologically by experienced paramedical workers. A skin smear was taken when there was any suggestion of multibacillary leprosy in the patient's history or symptomatology. All patients were biopsied at the most active site. The skin biopsy, fixed in 10% formalin, was sent to Antwerp. Sections were stained by the Trichrome Fite-Farracco technique.⁸

PB patients are defined as having clinical TT or BT leprosy with a bacteriological index of not more than 1 (Ridley scale, Pattyn *et al.*, 1981) at any site examined and confirmed as TT or BT leprosy by histopathology.

From 1980 to 1982, PB patients in Zaire, Rwanda and Burundi were classified according to accessibility, defined by the willingness to present once weekly at the treatment centre for 10 consecutive weeks. Accessible (acc.) patients were randomly allocated to one of the following treatment regimens:

Treatment A (TrA): RMP 1500 mg single dose, supervised, at the start of therapy, followed by 1 year DDS 100 mg daily, unsupervised.

Treatment B (TrB): RMP 900 mg once a week during 10 weeks, completely supervised.

Inaccessible (inacc.) patients received treatment A.

On the island of Anjouan all PB patients received treatment B-com: RMP 600 mg once a week for 10 weeks.

In the reference laboratory in Antwerp, and after treatment was started in the field, the patients were stratified according to previous treatment and clinical symptoms: less than 3 skin lesions (−3) and 3 or more skin lesions (+3).

The patients were followed clinically, bacteriologically (if indicated), and histopathologically. All patients analysed had a follow-up biopsy (FU1) at the same site as the initial one, 2 years after starting treatment, i.e. 1 year after the end of TrA, and 1 year and 9 months after the end of TrB and B-com. If FU1 showed no signs of leprosy, the subsequent follow-ups (FU) of the patients (at yearly intervals, starting from FU1) were done clinically, but if any symptom of aggravation was noted, at the moment of follow-up or at any other moment, a new biopsy was taken. If the FU1 biopsy still showed signs of leprosy, a biopsy was taken at yearly intervals until no more signs of leprosy were found.

For the present analysis only the histopathological results are taken into account. The efficacy of

the treatment regimens is evaluated by the proportion of patients cured, and by the relapse rate after cure. A cure is defined as the absence of histopathological signs of leprosy in any of the follow-up biopsies, irrespective of subsequent relapse. A relapse is defined as the reappearance of signs of leprosy in a biopsy after the initial histopathological cure: thus a relapse can only be diagnosed from the second FU biopsy onward.

Patients lost to follow-up were censored to the left, i.e. they were not counted when calculating the person years since the previous FU, because they had not been seen since that time.

For the calculations, relapses are considered to occur in the middle of the 1-year interval between two subsequent FU's. Statistical analysis was done by the Mantel-Haenszel χ^2 test for stratified samples, by the χ^2 test, with Yates' continuity correction for 2×2 tables, and by the Mantel-Haenszel χ^2 test for comparing rates. Confidence intervals are taken from *Tabulae Scientificalae*⁹.

Results

ZAIRE-RWANDA-BURUNDI: TREATMENTS A AND B

During 1980-82, 637 PB patients were started on the trial regimens A and B. Forty-two patients died of unrelated causes during the observation period, and 62 patients (9.7%) were lost to follow-up before FU2, leaving 533 patients for analysis.

Two hundred and fifteen patients were followed up to FU2, 192 patients up to FU3, and 126 patients up to FU4. There were no differences in follow-up between TrA and TrB groups ($0.8 > p > 0.7$). However, since FU1 took place 1 year after the end of TrA, but 1.75 years after the end of TrB, the mean follow-up period after the end of TrB is 0.77 year longer than for TrA (3.71 *vs* 2.94 years) among the accessible patients. Inaccessible patients were followed for a slightly shorter period than accessible patients with TrA, mean: 2.72 *vs* 2.94 years, difference not significant ($0.3 > p > 0.2$).

The probability of cure for each of the treatment regimens is summarized in Table 1. Among accessible patients, 33 (16.8%) of the 197 patients with TrA as well as 37 (19.0%) of the 195 patients with TrB had received some dapsone previously. Since no differences between previously treated and untreated patients were significant at the 5% level, these patients are taken together in all groups considered.

The cumulative probability of cure at FU4 is significantly higher ($0.01 > p > 0.005$) for all patients with TrB (0.9795) than for all patients with TrA (0.9188). However, among patients with less than 3 skin lesions TrA and TrB perform equally well ($0.7 > p > 0.6$). Only in patients with 3 or more skin lesions is TrB superior to TrA ($0.005 > p > 0.001$).

Among the inaccessible patients, there were 31 patients with less than 3 skin lesions, and 110 with 3 or more skin lesions, while 30 (21.3%) were previously treated. No differences in probability of cure, significant at the 5% level, were observed in relation to the number of skin lesions, nor in relation to previously treated or untreated status. Therefore all inaccessible patients are considered as one group.

The cumulative probability of cure at FU4 of inaccessible patients is comparable with that of all accessible TrA patients ($0.95 > p > 0.90$). However compared to all TrB patients TrA in inaccessible patients is inferior ($0.025 > p > 0.01$) as was the case in accessible patients. The speed of cure after stopping treatment is illustrated graphically in Figure 1.

In all groups taken together, there are 32 treatment failures: 16 in-patients followed up to FU2 (1 in group Acc. -3A, 8 in group Acc. +3A, 1 in group Acc. -3B, and 6 in group Finacc.), 13 in patients followed up to FU3 (6 in group Acc. +3A, 1 in group Acc. -3B, 2 in group Acc. +3B, and 4 in group Inacc.), and 3 in patients followed up to FU4 (1 in group Acc. +3A and 2 in Inacc.).

Of the 32 histopathological treatment failures, 24 (75%) showed considerable clinical

Table 1. Success of different bactericidal treatment regimens for paucibacillary patients in Zaire, Rwanda and Burundi

Group	t	n	c	% c	cum % c
Acc., -3, A	1	48	39	81	81
	2	9	4	44	89
	3	5	3	60	95
	4	2	1	50	97
Acc., +3, A	1	149	106	71	71
	2	43	18	41	83
	3	25	9	36	89
	4	16	1	6	89
Acc., -3, B	1-75	58	48	82	82
	2-75	10	8	80	96
	3-75	2	0		96
	4-75	2	0		96
Acc., +3, B	1-75	137	108	78	78
	2-75	29	18	62	91
	3-75	11	7	63	97
	4-75	4	2	50	98
Inacc., A	1	141	109	77	77
	2	32	13	40	86
	3	19	6	31	90
	4	13	1	7	91

Acc., accessible patients; Inacc., inaccessible patients; -3, less than 3 skin lesions; +3, 3 or more skin lesions; A, regimen A: RMP 1500 mg once, DDS 100 mg per day for 1 year; B, regimen B: RMP 900 mg once a week for 10 weeks; t, time (in years) after stopping treatment; n, number of patients not cured at the beginning of the follow-up interval; c, patients cured during follow-up interval; % c, percentage of patients cured during each interval; cum % c, cumulative percentage of cure.

improvement, 3 of them being considered clinically cured. In 7 patients (29.2%), the most recent pathological image showed signs of active leprosy, the remaining 17 showed inactive remnants (defined by the absence of epithelioid cells, or the presence of 3-5 epithelioid cells with a tendency to form a giant cell, together with traces of perineuritis or isolated granulomata consisting solely of lymphocytes). Three patients were given a single dose of RMP 40 mg/kg bodyweight and were consequently cured.

Six histopathological treatment failures showed no clinical improvement, and 2 got worse. Of these 8 cases without clinical improvement, 6 had signs of active leprosy in their most recent biopsy, and 2 showed remnant lesions. Three patients were given a single dose RMP 40 mg/kg bodyweight. Two were consequently cured. One patient did not respond to this second therapy, and was consequently treated with the combination DDS 100 mg + ETH 500 mg daily for 1 month, which was followed by cure.

The relapse rate is given in Table 2. Since relapse can occur only after a previous cure, which in this study was established at the earliest at FU1, the earliest that relapses can occur is between FU1 and FU2. It is therefore logical for the calculation of the number of person years of FU to take FU1

Figure 1. Probability of cure in relation to time after stopping treatment, according to accessibility, number of skin lesions and therapeutic regimen. Groups: see legend Table 1.

as the starting point. In this respect none of the differences observed between the groups is significant at the 5% level. Therefore, a global relapse rate, taking all groups together, is included. All relapses occur between FU1 and FU3. However, the 0 relapses per 66 person years between FU3 and FU4 are not significantly different from the 20 relapses per 363 person years between FU1 and FU3 ($0.2 > p > 0.1$).

The 95% confidence limits of the relapse rates per 100 person years, assuming a binomial distribution of the occurrence of relapse, are as follows: between FU1 and FU2: 1.54–5.15; between FU2 and FU3: 1.47–6.68; and between FU3 and FU4: 0–5.44.

All regimens were well tolerated. There were no hepatotoxicity or other side-effects. Upgrading reactions did occur more frequently in treatment group B than in treatment group A. They were discussed in detail previously for two of the participating centres.¹⁰ Observations in the other centres were comparable. Most reactions were mild to moderate and did not lead to increased neurological damage.

COMORES: TREATMENT B-COM

On Anjouan 367 PB patients were started on regimen B-com in 1981–82. Nineteen patients with

Table 2. Relapses occurring in paucibacillary patients after cure by different regimens

Group	FU	n	r	cens.	lc	ptys	Relapse rate per 100 person years
Acc., -3, A	2	39	1	0	4	38.5	2.60
	3	42	0	11	3	31	0
	4	34	0	26	1	8	0
			1			77.5	1.31
Acc., +3, A	2	106	3	0	18	104.5	2.87
	3	121	2	57	9	63	3.17
	4	71	0	51	1	20	0
			5			187.5	2.67
Acc., -3, B	2	48	1	0	8	47.5	2.11
	3	55	1	25	0	29.5	3.39
	4	29	0	22	0	7	0
			2			84.0	2.38
Acc., +3, B	2	108	2	0	18	107	1.87
	3	124	2	55	7	68	2.94
	4	74	0	48	2	26	0
			4			201	1.99
Inacc., A	2	109	5	0	12	106.5	4.69
	3	116	3	72	5	42.5	7.60
	4	46	0	40	1	6	0
			8			155	5.16
All	2	410	12	0	60	404	2.97
	3	458	8	220	21	234	3.42
	4	251	0	184	4	67	0
			20			705	2.84

Group, see legend Table 1; FU: time of evaluation: FU2=FU1+1 year, FU3=FU1+2 years, FU4=FU1+3 years, (FU1: 1 year after stopping treatment A, 1.75 years after stopping treatment B); n, number of patients cured at beginning of follow-up period; r, number of relapses during follow-up period; cens, number of patients censored during follow-up period (censoring to the left); lc, late cures: patients not cured at beginning of follow-up period, but cured at the end of it; ptys, patient years of follow-up during follow-up period; relapse rate, number of relapses per 100 patient years of follow-up.

lesions in the face were not biopsied at the start of treatment, 3 patients died of unrelated causes, 9 patients were lost to follow-up, and 17 patients were followed without histopathological examination. Of the remaining 319 patients, 292 were followed up to at least FU2. They are the subject of the present analysis. Eighty-five patients were followed up to FU2, 192 up to FU3, and 15 up to FU4. The mean follow-up period is 3.51 years. There is no difference during follow-up between previously treated and untreated patients, nor between patients with more or less than 3 skin lesions.

The probability of cure is summarized in Table 3. Regimen B-com is equally successful among previously treated and untreated patients as among patients with less than 3 (-3) and 3 or more (+3) skin lesions. Four of the treatment failures in group (-3) and 5 in group (+3) were followed up to FU2, and 2 treatment failures in group (-3) and 1 in group (+3) were followed up to FU3.

Table 3. Success of regimen B-com (RMP 600 mg 1/7 $\times$ 10) in PB patients on the island of Anjouan, République Fédérale Islamique des Comores

Group	t	n	c	% c	cum % c
-3	1.75	159	129	81	81
	2.75	30	20	66	93
	3.75	10	4	40	96
	4.75	6	0	0	96
+3	1.75	133	103	77	77
	2.75	30	18	60	90
	3.75	12	5	41	94
	4.75	7	1	14	95

Legend see Table 1.

Only 1 relapse was observed, in group (-3), between FU1 and FU2. The (-3) group has been followed for 263.5 person years. This gives a relapse rate of 0.38 per 100 person years (95% confidence interval: 0.01-2.10). Both groups together have been followed for 495.5 person years. Thus the relapse rate for all patients taken together is 0.20 per 100 person years (95% confidence interval: 0.01-1.12).

The regimen was well tolerated. No side-effects were observed. Upgrading reactions occurred in 3.4% of the patients, all in the (+3) group. All reactions were mild to moderate, and did not lead to increased neurological damage. In the (-3) group, all patients were classified as having 0 multilations¹¹ at all sites at the start of therapy and throughout their follow-up. In the (+3) group, 4 sites got worse by 1 degree, and 1 site by 2 degrees, for a total of 798 sites (6 sites per patient), while 31 sites got better by 1 degree, and 3 by 2 degrees. A comparison of the number of hypertrophied nerves at the start of treatment and at the last follow-up examination gives the following results: in the (-3) group, 43 patients (27%) had a decrease in hypertrophied nerves (by 1 to 4 nerves), while 10 patients (6.3%) had an increase (by 1 or 2 nerves); in the (+3) group, 60 patients (45.1%) had a decrease in hypertrophied nerves (by 1 to 5 nerves), and 2 patients (1.5%) had an increase (by 1 or 2 nerves).

Discussion

The present study was started when the results of a previous trial undertaken from 1977 on in Addis Ababa and Burundi (Warndorff *et al.* 1982) were still incomplete, and as there was some fear that 8 weekly 900 mg RMP doses would be insufficient, regimen B comprising 10 weekly 900 mg RMP doses was introduced. Regimen A was derived from a regimen studied by THELEP in MB patients (regimen C1: 1500 mg RMP followed by 2 years of daily DDS 100 mg) in which it showed clinically as efficient as more potent regimens. It is particularly suited for many situations in developing countries, since the single administration of RMP can be easily supervised while the tradition of DDS distribution is maintained.

It is much more difficult to evaluate the effect of treatment in PB than in MB leprosy since in the latter besides the clinical evolution, the BI and MI can be monitored and if a relapse is suspected it can be documented by mouse footpad inoculation. For the evaluation of treatment of PB leprosy the only parameters available are the clinical and histopathological evolution. The evolution of

neuritis and invalidities as far as it may be the result of reversal reactions is not a measure of the antibacterial activity of a treatment regimen, although it is eminently important for the patient. Sensitivity tests are not more discriminative since nerves may have been destroyed before therapy started. An important clinical sign of effective treatment is wrinkling of the affected skin sites, but it is not always present. Discoloration of the skin lesions is undoubtedly the least significant symptom as it may subside after a very long time or even not at all, becoming equivalent to a scar. In filariasis endemic areas, as is the case in some areas in Zaire, discoloration of the skin is particularly confusing, not only for the evaluation of treatment but also for the diagnosis.

Even the histological picture is not the ideal criterion. It does not reflect bacteriological events ideally. As was shown in a previous study¹² a short course efficacious therapy may leave PB granulomas in the skin during one year or more, as if they were the expression of removal of remaining antigen. Furthermore it is extremely difficult if not impossible to distinguish relapses from late reversal reactions, both on clinical grounds and on histopathology. However the goal of treatment being this disappearance of all lesions, the histology in PB leprosy is the most objective criterion available to document cure rates, and was therefore used in the present study. Since it had been shown previously¹² that PB granulomas in the skin rarely disappear by the first year after treatment, the first follow-up skin biopsies in the present studies were taken at 2 years after the start of therapy, this is at 1 and 1.75 years after the end of regimen A and B respectively.

All regimens tested perform satisfactorily. Even the least successful regimen of 1 year duration (Acc., + 3A) cures 90% of the patients within 4 years. Moreover, it should be noted that the present analysis considers the worst alternative, i.e. all patients censored as a 'no cure' are considered a failure. It cannot be excluded that some of these failures will be cured at a future follow-up. Thus, the figures presented here are minimal estimates, and the true probability of cure may be higher, e.g. for groups Acc. + 3A it could be as high as 0.96. (Calculation of additional cures: of the 25 patients in group Acc. + 3A, not cured at FU2, 8 are lost to follow-up. Of the remaining 17, 9 (52.94%) are cured at FU3, leaving 8 uncured, of these, 6 are lost to follow-up. 1 of the 2 remaining patients (50%) is cured at FU4. If we apply these probabilities of cure to the 25 patients not cured at FU2, we expect $25 \times 0.5294 = 13.2$ cures at FU3, leaving 11.8 uncured, of which $11.8 \times 0.5 = 5.9$ could be cured at FU4. Thus only 5.9 of the 149 patients in group Acc. + 3A would not be cured at FU4, giving a probability of $143.1/149 = 0.9604$.)

The present figures also stress the importance of the late cures. It is necessary to wait at least 3, or even 4 years after stopping treatment before evaluating the success of therapy in PB leprosy.

Among accessible patients in Zaire, Rwanda and Bunrundi, treatments A and B can be compared. They perform equally well in patients with less than 3 skin lesions, but in patients with 3 or more skin lesions, treatment B with its 10 doses of RMP is clearly superior to treatment A with its single dose of RMP. This suggests that for light cases, as evaluated by a limited number of skin lesions, a single dose of RMP will sufficiently boost immunity to permit the patient to get rid of the infection. For more severe cases the more intensive bactericidal regimen should be recommended. This regimen however requires a more rigorous supervision, and cannot be administered to inaccessible patients.

The results of TrA of inaccessible patients are comparable in terms of probability of cure to those among all accessible TrA patients taken together. This could be expected considering the proportion of patients in that group with more than 3 skin lesions (110 out of 141 = 78%). If the probabilities of cure of the acc. - 3A and the acc. + 3A groups are applied to the inaccessible patients, an expected probability of cure of 0.9169 is found (calculation:

$$\frac{(31 \times 0.9792) + (110 \times 0.8993)}{141}$$

this expected probability is very close to the observed 0.9149. This suggests that there is no difference between accessible and inaccessible patients in terms of probability of cure.

The relapse rates among the 4 accessible groups are comparable, but among the inaccessible

patients, twice as many relapses are observed, although statistical analysis does not permit to reject the hypothesis that the relapse rate is equal for all groups.

Strictly speaking, it is not justified to compare TrB-com with TrA and TrB. Not only was there no randomization, but in addition the epidemiologic situation on Anjouan is different from the one in Central Africa, as is illustrated by the following data: 49.2% of the patients on Anjouan were children (under 15 years of age) against 10.5% in Zaire, Rwanda and Burundi, and 54.5% of the patients on Anjouan had less than 3 skin lesions, against 10.5% in Zaire, Rwanda, Burundi. However, the data suggest that TrB-com is as effective as TrB in terms of probability of cure. The relapse rate is much lower, as well as the proportion of upgrading reactions. This may be connected with the epidemiologic differences mentioned.

Several studies in the literature cite relapse rates in paucibacillary patients after stopping DDS treatment. Some of these figures are difficult to interpret, since they do not take into account the patient years of observation, and cannot be considered 'true' rates. Five studies, giving relapse rates for varying periods of follow-up, are summarized in Table 4. Comparing the present study of these data from the literature, it is clear that a sudden stop of relapses after FU3 is not to be expected, however as shown previously¹³ 50% of relapses are expected to occur within the first 2 years after stopping treatment. It is also evident that the relapse rates in the present study are considerably higher than the rates reported in the literature. However, the studies cited report the appearance of clinical relapses, while in the present study relapses were diagnosed histopathologically, whereby the worst alternative was considered: if a patient had a biopsy with no signs of leprosy, which was followed by the biopsy showing histopathological presence of the disease, this was noted as a relapse. But often signs found in the positive biopsy, which was not always taken at exactly the same spot as the previous, negative one, were indicative of old, inactive or regressing disease.

Moreover, not all histopathological reappearance of signs of leprosy was accompanied by clinical aggravation, and in 2 patients where the clinical picture did deteriorate, it improved spontaneously later on. Thus, some of the relapses considered in the present study may in reality have been upgrading reactions. If clinical relapses only are considered, the present study finds 10 relapses, which gives an overall relapse rate of 1.42 per 100 person years. This is comparable to the relapse rates found during the first 4 years after stopping DDS. The higher relapse rate among

Table 4. Relapse rates per 100 patient years in paucibacillary patients after stopping DDS therapy

FU	Neelan ¹⁴	Vellut <i>et al</i> ¹⁵	Girdhar <i>et al.</i> ¹⁶	Jesudasan <i>et al.</i> ¹⁷	Pandian <i>et al</i> ¹⁸	Present study
1	2.03	0.8-2.3		1.29	0.57	—
2	2.33	1.1-2.5		1.36	0.53	2.97
3	2.63	0.5-1.8		0.61	0.61	3.42
4	1.41	0.8-1.3		0.13	0.50	0.00
5	—	0.3-0.7		0.56	0.58	
6	—	0.2-0.7		—	0.56	
7	—	0.4-0.8		—	0.52	
8	—	0.0-0.8		—	0.40	
9	—	0.0-0.3		—	0.21	
10	—	0.0-0.1	a b c	—	0.00	
Overall	2.16		3.1 2.6 2.7	0.97	0.53	2.84

FU, year after stopping treatment; a, overall relapse rate after stopping DDS at moment of inactivity; b, overall relapse rate after stopping DDS 18 months after moment of inactivity; c, overall relapse rate cited from Annual Report 1977 from the Central Leprosy Teaching and Research Institute, Chingleput.

inaccessible patients remains evident for clinical relapses also: 2.58 per 100 person years against 1.09 in all accessible patients taken together.

The present study suggests that intensive short-course bactericidal therapy results in a very high cure rate of paucibacillary patients, and an acceptably low relapse rate. Such therapy, with its easy logistics, low cost and high patient acceptability, is well suited for integrating leprosy control into the primary health care infrastructure.

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