

A 6 week quadruple drug regimen for the treatment of multibacillary leprosy

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Introduction

Although the WHO recommended multidrug therapy regimen for multibacillary (MB) leprosy is highly effective, there is a need from the operational point of view¹ to develop regimens of shorter duration.

We present here the results of a regimen of 6 weeks duration involving the supervised administration of four drugs, introduced in November 1989. Follow-up from 7 years on has become increasingly difficult as a result of political turmoil in the country. We therefore present the results as available.

Patients and methods

As in our previous studies,^{2–4} all patients were examined clinically, neurologically and bacteriologically; a copy of the clinical file was sent to Antwerp together with a skin biopsy fixed in 10% formalin. MB leprosy was defined as disease with a bacterial index (BI) of 2 or more at any of three sites from which slit-skin smears were prepared (one earlobe and two skin sites) and confirmed by histopathology.

Yearly follow-up examination identical to those at intake are performed. Patients received daily, 6 days a week, under supervision, rifampicin 600 mg, ofloxacin 400 mg, clofazimin 100 mg and once a week minocycline 100 mg.

For follow-up, patients were invited to present to the National Leprosy Centre in the capital or to the regional Health Centres, where they were examined by the mobile teams and actively searched for as far as possible. This became more and more difficult from year 7 on.

Relapses were suspected clinically when new active looking lesions appeared. These were

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confirmed by bacterial and histopathological examinations. All relapses had a BI of 4 or 5 with a proportion of solid staining bacilli after several negative BIs during the previous years.

The study was approved by the Ethical Committee of the Institute of Tropical Medicine, Antwerpen and the Ministry of Health of the Republic of the Comores.

Results

Between November 1989 and December 1993, a total of 136 patients giving their consent were taken into the study. At intake there were 18 (13.2%) patients with a BI = 2, 21 (15.4%) with a BI = 3, 73 (53.6%) with a BI = 4 and 24 (17.6%) with a BI = 5. All patients showed a rapid favourable clinical evolution. No major complications such as hepatitis or severe ENL requiring specific treatment were observed. No complaints of photophobia or skin discoloration were noted. As shown in Table 1, follow-up later than 6 years concerned considerably less than 50% of patients. The mean follow-up at year 6 was 4.7 years. During the first 6 years of follow-up, two relapses were diagnosed, at 56 and 60 months, respectively, after the start of treatment, giving rise to a cumulative relapse rate of 2%. Six more relapses were diagnosed at 72, 96, 96, 103, 106 and 111 months, respectively, after the start of therapy. Due to the small number of patients seen at 7–10 years of follow-up, calculations of cumulative relapse rates would be much misleading. At the start of therapy, the two patients relapsing at year 5 had a BI of 5. Among the six patients relapsing later, two had a BI of 4, the other had a BI of 5.

Table 1. Number of patients taken in the study, their follow-up and appearance of relapses

Years of follow-up	Number of patients	Cumulative number of patient years	Relapses		
			Number	Cumulative number	%
1	136	136	–		
2	124	260	–		
3	121	381	–		
4	106	487	–		
5	88	575	2	2	2
6	66	641	–	2	2
7	52	693	1	3	*
8	27	720	2	5	*
9	14	734	2	7	*
10	3	737	1	8	*
Mean (up to year 6)		4.7			

*Not calculated because low number of patients seen at the 7th year of follow-up.

Discussion

The antileprosy drugs of the 1980s, ofloxacin and minocycline,^{5–8} created new hopes for shorter treatment regimens in multibacillary leprosy. However, a treatment regimen consisting of the two drugs rifampicin and ofloxacin given daily for 4 weeks gave rise to an unacceptable high relapse rate of 2.9% or 11.5 per 100 patient years.^{9,10} In the present study, the quadruple regimen of daily rifampicin, ofloxacin, clofazimine and once weekly minocycline administered during 6 weeks, gave rise to a cumulative relapse rate of 2 per 100 patient years at year 6. Calculation of the relapse rate at years 7–10 when a continuously decreasing number of patients were seen would produce an unrealistic figure. In the absence of sufficient information concerning years 7–10 of follow-up, we cannot present a definitive result on the value of this regimen, only that it is superior to the 4 weeks daily rifampicin–ofloxacin evaluated at 5 years. It is noteworthy that in the present study, all relapsing patients had a BI of 4 or 5 at the start of treatment, as was the case in the study by Jamet *et al.*¹¹ Minocycline being a bactericidal^{8,12} and long acting drug against *Mycobacterium leprae*^{12,13} and in order to avoid possible unexpected side effects of the drug combination, it was decided in 1989 to administer minocycline only once a week. It is possible that daily administration of minocycline would enhance the bactericidal action of this regimen. No skin or oral pigmentation was observed. Indeed, these complications appear only after years of minocycline intake.^{14,15}

The strategy of multibacillary leprosy treatment has evolved along two main axes: either once monthly supervised treatment, completed by unsupervised drug intake, but for long duration, originally 24 months, now reduced to 12 months¹ or daily drug intake of shorter duration. The Antwerp laboratory¹⁶ has been involved in studies of treatment regimens lasting 52, 34, 13 and 4 weeks duration, all involving only the drugs of the 1970s: rifampicin, ethionamide, dapsone or clofazimine. These studies showed that some regimens may be very promising during the first 5 years of follow-up but may give rise to cumulative relapse rates of 4 per 100 patient years at 8–9 years of follow-up.¹⁶ The interpretation could be that ‘early’ relapses appearing during the first 5 years of follow-up are due to insufficient killing of originally actively multiplying organisms, while late relapses could be due to revival of dormant bacilli that resist all chemotherapeutic agents currently in use. Wayne¹⁷ and Wayne *et al.*^{18,19} showed that slow depletion of oxygen permits tubercle bacilli to adapt to a non-replicating state under microaerophilic conditions and enhance their ability to survive anaerobic conditions. This could account for long term latency of tuberculosis in the human host. Efforts to eradicate these bacteria should include agents killing these in both microaerophilic and anaerobic non-replicating stages. If this hypothesis of Wayne, sustained by experimental evidence, concerning *M. tuberculosis* is correct, and holds also for *M. leprae*, other fluoroquinolones active against anaerobes, such as clinafloxacin or trovafloxacin, should be studied in the treatment of leprosy in mice and in humans.

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