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NEWER DRUGS IN LEPROSY

Prof. Jacques H. Grosset
Professor Emeritus
Laboratoire de Bacteriologie
Faculte de Medecine Pitie-Salpetriere
75634 Paris 13, France

Despite the fact that the combined drug regimens recommended by the WHO Study Group ([31]) in the fall of 1981 for leprosy control programs have demonstrated their effectiveness, research in the therapy of leprosy is still needed. As already emphasized at the Orlando Congress ([9]) operational and health system research should be conducted to improve delivery of drugs, compliance of patients and medical staff to the full implementation of the prescribed drug regimens and to assess their long-term results. In addition to these basic needs, the control programs would benefit from simplification and shortening of the presently available drug regimens in order to make them easily dispensed and observed by the general health services. A means by which such an objective can be reached is to take advantage of the newly discovered drugs active against *Mycobacterium leprae* for developing drug regimens with bactericidal activities more powerful than those of the standard regimens. That objective appears within arm's reach.

Discovery of new drugs active against *M. leprae*. After the combined drug regimens were recommended by the WHO Study Group, screening of antileprosy drugs, conducted almost exclusively in the mouse foot pad model of *M. leprae* infection ([28]), continued. Since the mid-1980s, the bactericidal activities of the new fluoroquinolones, pefloxacin and ofloxacin ([5, 10, 12, 25, 27]), a new macrolide, clarithromycin ([4, 17]), and a cycline, minocycline ([6, 17]) have been demonstrated. All of these drugs were able to apparently cure the limited experimental leprosy infection in the mouse model after only a single month of therapy. Compared to dapsone and clofazimine, the bactericidal activities of the new drugs were thus considerable. Only rifampin was more powerful than the new drugs against *M. leprae* in the mouse model ([20]).

Because of their experimental activities, the new drugs were tested in humans with multibacillary (MB) leprosy, the only leprosy patients in whom the microbial load is large enough to permit a precise assessment of the antimicrobial activity of a drug. As shown in Table 1, the new fluoroquinolones were killing more than 99.99% of the viable *M. leprae* after only 4 weeks of therapy, confirming the findings in the mouse model ([11, 18, 24]). Since ofloxacin given at a daily dose of 400 mg was as potent as pefloxacin given at a daily dose of 800 mg, the former drug was considered more suitable as an antileprosy drug than the latter. In addition, the combination of ofloxacin with dapsone and clofazimine was neither antagonistic nor additive, indicating that the overall bactericidal effect was that of the most potent compound, opening a door to an effective new three-drug regimen for patients with rifampin-resistant *M. leprae*. Almost similar bactericidal activities were demonstrated (Table 2) with minocycline ([7, 14]) and clarithromycin ([14]).

Fully supervisable, monthly administered regimen. Because of the powerful bactericidal activities against *M. leprae* of ofloxacin and clarithromycin given daily for only a month, the prospect of developing fully monthly administered drug regimens became a reality. Because the role of the drugs combined with rifampin was mainly to prevent the selection of a rifampin-resistant mutant, the next step was to assess the bactericidal activities of a single dose of the new drugs given alone or in combination ([8, 15, 21]). In the mouse model, a single pulse of the combination minocycline-clarithromycin was killing 96% of viable *M. leprae;* whereas a single pulse of

TABLE 1 *Bactericidal activities of daily pefloxacin and ofloxacin against* M. leprae *in humans (Adzopé trials).*

Trial's author (ref)	Drug regimen	Killing activity
N'Deli, *et al.*, 1990 ([24])	Pefloxacin 800	>99% (in 2 months)
Grosset, *et al.*, 1990 ([11])	Pefloxacin 800 versus Ofloxacin 400	99.99% (in 4 weeks)
Ji, *et al.*, 1994 ([18])	Ofloxacin 400 versus Ofloxacin 800 versus Oflo 400 + DDS + CLO	>99.99% (in 4 weeks)

the three-drug combination minocycline-clarithromycin-ofloxacin was killing 98.4% of viable *M. leprae,* a bactericidal effect close to the 99.5% killing effect of a single dose of rifampin ([19, 32]). The addition of the three drugs to rifampin neither increased the bactericidal activity of rifampin nor antagonized it. It was concluded that the combination of a single pulse of minocycline-clarithromycin-ofloxacin with rifampin would kill rifampin-resistant mutants as well as rifampin-susceptible *M. leprae.* As a result, the bactericidal activity of a single dose minocycline-clarithromycin-ofloxacin was tested in patients with MB leprosy in comparison with a single pulse of rifampin alone and 1 month standard multidrug therapy (MDT) (one dose rifampin plus daily dapsone and clofazimine for 4 weeks). The antibacterial effect of the three-drug combination was similar to that observed in the mouse model, but 45% of the patients experienced gastro-intestinal side effects related to the use of clarithromycin ([15]). Although there were no abnormal hepatic and renal function tests, the side effects were sufficient to preclude the routine use of clarithromycin in the field.

Experiments were, therefore, focused on the assessment of the bactericidal activity against *M. leprae* of the combination ofloxacin-minocycline in the mouse model, both drugs being given at dosages equipotent in the mouse to the dosages used in man ([26]). The killing activity of a single pulse ofloxacin-minocycline against *M. leprae* was 50%–60% compared with the 96% killing of single-pulse rifampin alone, and the 96.8% killing of the three-drug combination rifampin-ofloxacin-minocycline ([21]). In humans, a single pulse of the combination ofloxacin 400 mg + minocycline 100 mg was killing 68% to 98% of viable *M. leprae,* and a single pulse of the three-drug combination rifampin 600 mg + ofloxacin 400 mg + minocycline 100 mg was killing more than 99% of viable *M. leprae* ([21]).

Such impressive results led to the clinical assessment in the field of the three drugs given as a single-dose combination known as ROM (rifampin-ofloxacin-minocycline) for the therapy of single-lesion paucibacillary (PB) leprosy ([29]). The trial was conducted as a double-blind, control, clinical trial among 1483 patients from September 1994 to July 1995, the control regimen being the standard 6-month WHO regimen with daily 100 mg dapsone and 6 monthly doses of 600 mg rifampin. The efficacy assessment was on clinical grounds and was performed 1 year after completion of the trial. As shown in Table 3, 99.1% of the patients exhibited clinical improvement in both arms of the trial. However, those patients with marked clinical improvement were slightly but significantly more fre-

TABLE 2. *Bactericidal activities of daily 100 mg minocycline in MB leprosy patients.*

Study's author	Total patients	No. patients with *M. leprae* infective in mice after		
		1 mo.	2 mos.	3 mos.
Gelber, 1993 ([7])	8	5/8	2/8	0/8
Ji, *et al.*, 1993 ([14])	11	1/11	0/11	0/11

TABLE 3. *Response to single-dose ROM in the single-lesion multicenter trial. ([29])*

Clinical improvement	ROM (N = 697)	WHO (N = 684)
None	0.9%	0.9%
Any	99.1%[a]	99.1%[a]
Marked	51.8%[b]	57.3%[b]

[a] p = 1.
[b] p = 0.04

quent in the standard 6-month WHO arm. Considering the operational advantage of a single-pulse ROM over the 6-month standard therapy, the Seventh Report of the WHO Expert Committee on Leprosy ([30]) recommended in 1997 the use of single-dose ROM for the treatment of patients with single-lesion PB leprosy.

Recent progress toward a much more effective drug regimen. In the last few years, two antimicrobial drugs, namely, moxifloxacin and rifapentine, have been identified or re-identified ([13]) as having highly promising antimycobacterial activities ([16, 22]). Moxifloxacin is a fluoroquinolone, whose activity against *M. tuberculosis* is similar to or slightly better than that of sparfloxacin ([16]), and is, therefore, much more powerful than ofloxacin and even its levogyre constituant, levofloxacin. For example, in the mouse model on a weight to weight basis, 50 mg/kg sparfloxacin or moxifloxacin were more powerful than 300 mg/kg ofloxacin ([23]) against *M. tuberculosis.* In addition, in the same model 50 mg/kg moxifloxacin were as powerful as 25 mg/kg isoniazid. Moxifloxacin has no reported phototoxicity, perhaps because its molecule contains only a single fluorine atom and not two as that of sparfloxacin. In humans, the daily dose of moxifloxacin is 400 mg for adults. Of course, there is cross-resistance between moxifloxacin and other fluoroquinolones.

The second drug, rifapentine, is a long lasting rifamycin derivative, the serum half-life of which is three times longer than that of the parent compound rifampin ([22]). The minimal inhibitory concentration (MIC) of rifapentine against *M. tuberculosis* is similar or one dilution inferior to that of rifampin. Since there is cross-resistance between rifapentine and other rifamycin derivatives, the advantage of rifapentine over rifampin lies only in its pharmacokinetic properties. In mice infected with *M. tuberculosis* ([1]) and in tuberculosis patients, once weekly rifapentine is only marginally less active than daily rifampin, both drugs being given at the same dosage of 10 mg/kg.

TABLE 4. *Bactericidal activity against* M. leprae *of a single-dose moxifloxacin and rifapentine in the mouse.*

Regimen[a]	% Viable	*% M. leprae* killed by treatment
Untreated control	21.82	–
OFLO	8.69	60.2[b b]
MOXI	1.73	92.1[b b]
OFLO + MINO	5.48	74.9[c c]
MOXI + MINO	1.38	93.7[c c]
RMP	1.73	92.1[c d]
RPT	0.09	99.6[d d]
RMP + OFLO + MINO	1.09	95.0[d e]
RPT + MOXI + MINO	0.02	99.9[d e]

[a] OFLO = Ofloxacin 150 mg/kg; MOXI = moxifloxacin 150 mg/kg; RMP = rifampin 10 mg/kg; RPT = rifapentine 10 mg/kg; MINO = minocycline 25 mg/kg.
[b] $p < 0.002$. [c] $p < 0.05$. [d] $p < 0.001$. [e] $p < 0.001$

Because of the potential benefit to substitute rifapentine (P) for rifampin (R) and moxifloxacin (Mx) for ofloxacin (O) in the single-dose ROM combination, the bactericidal activities of P and Mx were measured in the mouse foot-pad model of leprosy ([3]). Precisely using the proportional bactericidal test ([2]), the bactericidal activities of P alone and Mx alone, of the combinations Mx-minocycline (M) and PMxM were compared with those of R alone and O alone, and those of OM and ROM, all drug regimens being given as single-dose therapy. The results (Table 4) were surprisingly promising: a) a single dose of 10 mg/kg P killed 20 times more *M. leprae* than a single dose of 10 mg/kg R; b) a single dose of 150 mg/kg Mx, equipotent to 400 mg in man, killed 5 times more *M. leprae* than 150 mg/kg O, and as much as 10 mg/kg R; c) a single dose of the three-drug combination PMxM killed 50 times more *M. leprae* than a single dose of ROM. Heretofore, no rifampin-containing multidrug regimen had been found to be more bactericidal than rifampin alone, either in the mouse model ([20]) or in man ([21]), presumably because the ac-

tivities of all accompanying drugs were relatively weak compared to that of rifampin. Since the combination PMxM was more bactericidal than RPT alone ($p < 0.05$), one may conclude that the addition of MxM enhanced the activity of P, probably because of the rather powerful bactericidal activity of Mx.

To confirm the promising bactericidal activities against *M. leprae* of P and Mx in humans and, more importantly, to promote the development of the combination PMxM as a potentially much more active substitute for ROM, a short-term clinical trial of single-dose PMxM single-dose ROM is being conducted among patients with lepromatous leprosy.

SUMMARY

During the last 15 years, new drugs active against *Mycobacterium leprae* have been identified. All of them belong to the fluoroquinolone, cycline and macrolide drug families. In the mouse model and in humans, minocycline, ofloxacin, and clarithromycin have demonstrated, individually or in combination, antileprosy activities much superior to those of the standard drugs dapsone and clofazimine. In humans, a single dose of the combination ofloxacin 400 mg + minocycline 100 mg was able to kill 68% to 98% of viable *M. leprae* and a single dose of ROM, a three-drug combination of rifampin 600 mg + ofloxacin 400 mg + minocycline 100 mg, was killing more than 99% of viable *M. leprae*. As a result of a double-blind, control, clinical trial, the Seventh Report of the WHO Expert Committee on Leprosy recommended in 1997 the use of single-dose ROM for the treatment of patients with single-lesion paucibacillary leprosy. Recently moxifloxacin, a new fluoroquinolone, and rifapentine, a long-lasting rifamycin derivative, have demonstrated in the mouse model highly promising antileprosy activities, justifying their assessment in humans.

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