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The Diarylquinoline R207910 Is Bactericidal against *Mycobacterium leprae* in Mice at Low Dose and Administered Intermittently▽

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The diarylquinoline R207910 is profoundly bactericidal in a murine model of tuberculosis. Previously, R207910 was also found to be bactericidal for *Mycobacterium leprae*-infected mice during lag phase. Herein we evaluate the bactericidal efficacy of R207910 (1 to 120 mg/kg of body weight) when administered five times weekly, once weekly, and once monthly during logarithmic multiplication of *M. leprae* organisms. All treatments were found to be bactericidal, suggesting that both low and intermittent dosing with R207910 holds promise for leprosy patients.

The diarylquinoline R207910 (also known as TMC207) represents a new class of antimicrobials uniquely active against mycobacteria, killing mycobacteria in vitro by blocking energy production (1). In vitro, R207910 has been found to inhibit a wide range of *Mycobacterium tuberculosis* clinical isolates and other mycobacterial species (1). In murine tuberculosis, daily administration of R207910 alone exceeds the bactericidal activity of the standard WHO regimen (isoniazid, rifampin [rifampicin], and pyrazinamide) (1). Also a combination with rifapentine and pyrazinamide given once weekly proved to be more active than the daily regimen recommended by the WHO (22). R207910 has several virtues that heighten its promise for the therapy of tuberculosis, such as a low MIC and a low minimal bactericidal concentration (1), demonstrable activity against nonreplicating *M. tuberculosis* organisms (15), and a prolonged plasma half-life in human volunteers (1).

Previously, Ji et al. (14) demonstrated that single doses of 25 mg/kg of body weight or 100 mg/kg given 1 day after infection of mice with *Mycobacterium leprae* (i.e., during lag phase) were equally bactericidal and that the bactericidal activity was equipotent to those of rifampin, rifapentine, and moxifloxacin while being superior to those of minocycline, PA-824, and linezolid. In order to further evaluate the activity of R207910 and assess different doses and frequencies of administration, we initiated a dose fractionation study wherein the activity of R207910 against *M. leprae* in infected mice was evaluated by a different technique, the standard kinetic method of Shepard (19). In this protocol, CBA/J mice were infected in both hind footpads with 5,000 *M. leprae* organisms and orally treated by gavage during logarithmic multiplication from day 60 to day 150 after infection with several dosage schedules of R207910, formulated in 20% hydroxypropyl-ß-cyclodextrin.

Study mice were (i) untreated (controls); (ii) treated five times weekly with 1 mg/kg, 3 mg/kg, 6 mg/kg, 12.5 mg/kg, and 25 mg/kg for 3 months; (iii) treated once weekly with 25 mg/kg, 30 mg/kg, 50 mg/kg, and 100 mg/kg for 3 months; and (iv) treated once monthly with 25 mg/kg, 50 mg/kg, 100 mg/kg, and 120 mg/kg (three doses). Keeping in mind that for murine tuberculosis the total weekly dosage has been shown to be the driver of activity, irrespective of the frequency of administration (22), we specifically designed several dosage schedules to deliver the same monthly dose of R207910. *M. leprae* organisms were enumerated in hind footpad pools (two mice, four feet) at the completion of therapy (day 152) and 3 months later (day 238), as well as on days 302 to 363 for some groups. With the kinetic method, if $\geq 10^5$ *M. leprae* organisms are obtained, growth is considered to have occurred. If growth is obtained at the completion of therapy, the treatment is considered to be inactive. If growth of *M. leprae* is not obtained at completion of therapy but is soon thereafter, activity is considered bacteriostatic, and if growth is further suppressed, bactericidal activity is considered to have occurred (19).

In all control mice, *M. leprae* growth ($\geq 10^5$ organisms per footpad) was confirmed on day 152 (completion of therapy) and reached levels greater than 10^6 organisms on days 228 and 338 (Table 1). On the other hand, growth was not found in any of the mice treated with any dosage of R207910, either on day 152 or on day 228, a result demonstrating that all dosage schedules were bactericidal for *M. leprae*. Furthermore, evidence for prolonged prevention of multiplication and for the bactericidal activity of R207910 (as assessed on days 302 to 363) was obtained for several groups treated once weekly and once monthly. Five weekly doses of R207910 as low as 1 mg/kg (approximately 25 mg/kg per month) were found to be as bactericidal for *M. leprae* as a single monthly dose of 25 mg/kg.

Our findings extend those of Ji et al. (14) demonstrating that R207910 is bactericidal for *M. leprae* during logarithmic multiplication at low five-times-weekly doses and even when administered once weekly or once monthly. Although bactericidal activity for *M. leprae* in mice (6, 7, 10–13) generally translates well to leprosy patients (3–5, 9), this is not always the case, as, for example, with clofazimine (8, 20).

Currently, for the most severe multibacillary form of leprosy, the WHO (23) recommends monthly supervised rifampin (600 mg) and clofazimine (300 mg) and unsupervised daily dapsone

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TABLE 1. Multiplication of *M. leprae* organisms in mice

R207910 dose (mg/kg)	Frequency	No. of *M. leprae* organisms/footpad on day 152	Growth[a] of *M. leprae* found on day 152	No. of *M. leprae* organisms/footpad on day 228	Growth of *M. leprae* found on day 228	No. of *M. leprae* organisms/footpad found on days 302–365[b]	Growth of *M. leprae* found on days 302–365
None		1.6×10^5	+	1.2×10^6	+	1.0×10^6 (336)	+
1	Five times weekly	$\leq 10^4$	−	$\leq 10^4$	−		
3	Five times weekly	$\leq 10^4$	−	$\leq 10^4$	−		
6	Five times weekly	$\leq 10^4$	−	$\leq 10^4$	−		
12.5	Five times weekly	$\leq 10^4$	−	$\leq 10^4$	−		
25	Five times weekly	$\leq 10^4$	−	$\leq 10^4$	−		
25	Once weekly	$\leq 10^4$	−	$\leq 10^4$	−		
30	Once weekly	$\leq 10^4$	−	$\leq 10^4$	−	$\leq 10^4$ (320)	−
50	Once weekly	$\leq 10^4$	−	$\leq 10^4$	−	$\leq 10^4$ (302)	−
100	Once weekly	$\leq 10^4$	−	$\leq 10^4$	−	$\leq 10^4$ (363)	−
25	Once monthly	$\leq 10^4$	−	$\leq 10^4$	−		
50	Once monthly	$\leq 10^4$	−	$\leq 10^4$	−	$\leq 10^4$ (347)	−
100	Once monthly	$\leq 10^4$	−	$\leq 10^4$	−		
120	Once monthly	$\leq 10^4$	−	$\leq 10^4$	−	$\leq 10^4$ (347)	−

[a] Growth was present (+) if $\geq 10^5$ *M. leprae* organisms per footpad were observed.
[b] Numbers in parentheses are the actual numbers of days after footpad infection when the number of *M. leprae* organisms was assessed.

(100 mg) and clofazimine (50 mg) for 1 year. In tuberculosis chemotherapy, it has become clear that two or more bactericidal agents are required to obtain effective short-course regimens (2), and the shortest effective regimen for tuberculosis, 6 months, still undesirably long, requires the incorporation of two agents active against nonreplicating bacilli, namely, rifampin and pyrazinamide. Directly observed and supervised therapy is considered essential for the successful treatment of tuberculosis (16) and, by extension, leprosy. In this regard, intermittent treatment would prove operationally advantageous for both mycobacterial diseases, the currently recommended regimen for leprosy being only partially supervised. The potential for even greater intermittency in the treatment of leprosy, possibly once monthly, may result from the longer generation time of *M. leprae* than that of *M. tuberculosis*, respectively, 2 weeks in vivo and 1 day in vitro. The key component of the current WHO therapy for the most-severe cases of leprosy is rifampin (18, 21), which is its only bactericidal agent (20), and monthly administration of that regimen is generally successful. Thus, perhaps leprosy treatment would be more amenable to monthly treatment than would tuberculosis, for which weekly treatment might be the limit. The recent demonstration that moxifloxacin (17) is as bactericidal for *M. leprae* in leprosy patients as is rifampin opens the prospect of combining two truly bactericidal agents.

Ideally, a new-generation regimen to treat leprosy would be bactericidal in patients, active when administered intermittently, and effective against nonreplicating organisms. Rifampin measures up in all three regards. R207910 has been demonstrated to be active in vitro against nonreplicating tuberculosis bacilli (15), and herein we have demonstrated with murine leprosy that it is bactericidal even when administered once monthly.

From the earlier results of Ji et al. (14) and the current study, R207910 merits a trial with leprosy patients, once more long-term human safety data have become available. If it proves similarly bactericidal for *M. leprae* in patients, its inclusion in a new-generation regimen holds the potential for a monthly fully supervised regimen with a shorter duration than that currently required.

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