RESEARCH LETTER

Risk of Immunologic Reactions During Monthly Therapy for Hansen Disease

Leprosy, or Hansen disease (HD), is a chronic granulomatous infection caused by the *Mycobacterium leprae* complex.[1] It predominantly affects the skin and peripheral nerves, with manifestations determined by the host's cellular immune response.[1] Disability often results from immunologic reactions (IRs), including type 1 reaction (T1R) or reversal reaction and erythema nodosum leprosum (ENL) or type 2 reaction, which cause neuritis and subsequent nerve damage.[2]

Supplemental content

World Health Organization (WHO) guidelines recommend multidrug therapy (MDT), comprising monthly rifampin and daily dapsone and clofazimine, based on large clinical studies.[2] While effective, MDT's high pill burden and adverse effects can impair adherence. In a preclinical model, a single dose of rifampin, moxifloxacin, and minocycline (RMM) eliminated 99.9% of viable *M leprae*.[3] A randomized clinical trial of patients with paucibacillary disease demonstrated similar effectiveness between MDT and monthly RMM therapy.[4] Although controversial,[5] RMM

Table 1. Demographic, Disease, and Immunologic Reaction Characteristics of Patients With Hansen Disease

Characteristic	Patients, No. (%)	
	MDT (n = 86)	RMM therapy (n = 25)
Demographic		
Age at diagnosis, mean (range), y	52.1 (15-85)	51.4 (28-90)
Sex		
Male	54 (63)	15 (60)
Female	32 (37)	10 (40)
Ethnicity[a]		
Hispanic or Latino	37 (43)	10 (40)
Non-Hispanic or Latino	45 (52)	14 (56)
Unknown or not reported	4 (5)	1 (4)
Race[a]		
Asian	2 (2)	0
Black or African American	8 (9)	3 (12)
White	72 (84)	22 (88)
Unknown	4 (5)	0
Disease		
WHO classification		
Multibacillary	56 (65)	22 (88)
Paucibacillary	30 (35)	3 (12)
Ridley-Jopling criteria		
Lepromatous leprosy	10 (12)	7 (28)
Borderline lepromatous leprosy	43 (50)	14 (56)
Borderline borderline leprosy	4 (5)	1 (4)
Borderline tuberculoid leprosy	26 (30)	1 (4)
Tuberculoid leprosy	2 (2)	2 (8)
Indeterminate leprosy	1 (1)	0
Immunologic reaction		
T1R	53 (62)	9 (36)
Duration of T1R symptoms, mean (SD), mo	11.6 (19.2)	9.5 (14.7)
Immunosuppressants for T1R, mean (SD)	1.4 (0.95)	1.3 (0.86)
Patients requiring immunosuppression for T1R	43 (81)	8 (88)
Duration of immunosuppression for T1R, mean (SD), mo	25.5 (27.9)	17.1 (16.5)
ENL	25 (29)	12 (48)
Duration of ENL symptoms, mean (SD), mo	18.9 (26.3)	17.1 (17.9)
Immunosuppressants for ENL, mean (SD)	2.4 (0.99)	2.7 (1.48)
Patients requiring immunosuppression for ENL	24 (96)	11 (92)
Duration of immunosuppression for ENL, mean (SD), mo	37.6 (33.2)	22.1 (19.0)

Abbreviations: ENL, erythema nodosum leprosum; MDT, multidrug therapy; RMM, rifampin, moxifloxacin, and minocycline; T1R, type 1 reaction; WHO, World Health Organization.

[a] Race and ethnicity were self-reported and obtained from the electronic health record. These data were included in this analysis to characterize the study population.

Table 2. Firth Logistic Regression Analysis of Risk Factors for Type 1 Reaction (T1R) and Erythema Nodosum Leprosum (ENL)

Variable and reaction type	β Coefficient (SE)	OR (95% CI)	*P* value
Intercept			
T1R	−1.00 (0.91)	0.37 (0.05-2.05)	.26
ENL	−2.21 (1.12)	0.11 (0.01-0.89)	.04
Age			
T1R	−0.01 (0.01)	0.99 (0.96-1.02)	.44
ENL	−0.03 (0.02)	0.98 (0.94-1.01)	.10
Male vs female			
T1R	−0.42 (0.49)	0.66 (0.25-1.71)	.39
ENL	0.54 (0.58)	1.72 (0.55-5.95)	.36
BT + BB + BL vs other[a]			
T1R	2.14 (0.72)	8.48 (2.33-46.42)	.001
BL + LL vs other[b]			
ENL	2.48 (0.86)	11.9 (2.71-112.89)	<.001
RMM therapy vs MDT			
T1R	−1.29 (0.67)	0.28 (0.06-0.98)	.047
ENL	−0.12 (0.69)	0.89 (0.19-3.38)	.86

Abbreviations: BB, borderline borderline leprosy; BL, borderline lepromatous leprosy; BT, borderline tuberculoid leprosy; LL, lepromatous leprosy; MDT, multidrug therapy; OR, odds ratio; RMM, rifampin, moxifloxacin, and minocycline.

[a] Other included BT + BB + BL and TL + LL.

[b] Other included BL + LL and TL + BT + BB.

therapy is now the regimen recommended by the National Hansen's Disease Program (NHDP) despite limited clinical studies. One concern is the IR risk associated with RMM therapy. To address this concern, we analyzed differences in T1R and ENL in patients receiving MDT vs RMM.

Methods | This retrospective cohort study included patients with biopsy- and polymerase chain reaction–confirmed HD treated at Jackson Memorial Hospital HD Clinic (Miami, Florida) between October 1, 2010, and November 30, 2025. The University of Miami Institutional Review Board approved this study and waived the informed consent requirement because the study posed minimal risk. We followed the STROBE reporting guideline.

Patients were treated according to NHDP guidelines. During data synthesis, patients were grouped under MDT or RMM therapy based on their original treatment regimen. Risk of T1R or ENL was modeled using logistic regression, controlling for leprosy classification (WHO, Ridley-Jopling), age at diagnosis, and sex. Patients presenting with IR before start of RMM therapy or MDT were excluded. As a categorical variable, we used the borderline tuberculoid, borderline borderline, or borderline lepromatous disease status for T1R and the borderline lepromatous or lepromatous leprosy disease status for ENL.

Firth logistic regression and likelihood ratio test were conducted in R, version 2024.12.0+467 (RStudio) (eMethods in Supplement 1). Two-sided $P < .05$ indicated statistical significance.

Results | The 111 patients in the cohort had a mean (range) age at diagnosis of 52 (15-85) years and included 69 males (62%) (**Table 1**). Among these patients, 78 (70%) had multibacillary disease per WHO guidelines, while 57 (51%) had borderline lepromatous and 27 (24%) had borderline tuberculoid leprosy per Ridley-Jopling criteria (Table 1). Eighty-six patients (77%) received MDT and 25 (23%) received RMM, although 11 (10%) switched from MDT to RMM.

T1R occurred in 62 patients (56%), with a median (IQR) onset 2 (0-10) months after initiating antibiotics. ENL occurred in 37 patients (33%), with a median (IQR) onset of 1 (0-7.5) month. Thirteen patients (12%) experienced more than 1 IR. Compared with MDT, RMM therapy was associated with significantly decreased risk of T1R (odds ratio [OR], 0.28; 95% CI, 0.06-0.98; $P = .047$) (**Table 2**). In contrast, RMM therapy compared with MDT was not associated with ENL risk (OR, 0.89; 95% CI, 0.19-3.38; $P = .86$). No significant differences were found in IR frequency, symptom duration, or immunosuppressant use (Table 1).

Discussion | While MDT has been the gold standard therapy for leprosy globally, in 2025 the NHDP changed their treatment recommendations to monthly RMM therapy for both paucibacillary and multibacillary disease. Leprosy experts have raised concerns regarding RMM therapy, including lack of sufficient evidence in patients with multibacillary disease and potential increase in IR risk given the anti-inflammatory role of daily antibiotics.[5,6]

To our knowledge, this study was the first to demonstrate a significantly lower risk of T1R in patients receiving RMM vs MDT (OR, 0.28; 95% CI, 0.06-0.98) and no significant difference in ENL risk. While T1R reflects heightened cell-mediated immunity to *M leprae* complex antigens, ENL is primarily immune complex mediated.[2] Monthly therapy may minimize sustained antigen release, leading to lower rates of delayed hypersensitivity reactions. ENL is associated with increased morbidity and is often more difficult to manage, requiring prolonged courses of immunosuppressive medications; therefore, the lack of increased risk in our cohort is also an important finding.[7]

While prospective, head-to-head trials are needed to establish the effectiveness and microbiological outcomes of RMM therapy in multibacillary disease, this study provided some reassurance regarding its decreased risk of T1R, although this finding must be interpreted with caution given the limited

sample size. Another study limitation is the T1R regression model was constrained by the small number of events in the RMM therapy group; thus, OR estimates may be unstable. Additional limitations include retrospective design, single-center scope, and shorter follow-up for the RMM therapy group, which may underestimate delayed IR.

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