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Ofloxacin-Containing Multidrug Therapy in Ambulatory Leprosy Patients: A Case Series

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Abstract

Background: Standard dapsone and clofazimine-containing multidrug therapy (MDT) for leprosy is limited by drug tolerability, which poses treatment adherence barriers. Although ofloxacin-based regimens are promising alternatives, current efficacy and safety data are limited, particularly outside of endemic areas. We evaluated treatment outcomes in patients with leprosy receiving ofloxacin-containing MDT (OMDT) at our center.

Methods: We performed a retrospective chart review of patients treated for leprosy at our center over an 8-year period (2011-2019). Primary outcomes evaluated were clinical cure rate, occurrence of leprosy reactions, antibiotic-related adverse events, and treatment adherence. Analyses were descriptive; however, data were stratified by age, sex, spectrum of disease, region of origin, and treatment regimen, and odds ratios were reported to assess associations with adverse outcomes.

Results: Over the enrolment period, 26 patients were treated with OMDT (n = 19 multibacillary, n = 7 paucibacillary), and none were treated with clofazimine-based standard MDT. At the time of analysis, 23 patients (88%) had completed their course of treatment, and all were clinically cured, while 3 (12%) were still on treatment. Eighteen patients (69%) experienced either ENL (n = 7, 27%), type 1 reactions (n = 7, 27%), or both (n = 4, 15%). No patients stopped ofloxacin due to adverse drug effects, and there were no cases of allergic hypersensitivity, tendinopathy or rupture, or *C. difficile* colitis.

Conclusions: We demonstrate a high cure rate and tolerability of OMDT in this small case series over an 8-year period, suggesting its viability as an alternative to standard clofazimine-containing MDT.

Keywords

fluoroquinolones, leprosy, *Mycobacterium leprae*, neglected tropical diseases, peripheral neuropathy, type 1 reaction

Introduction

Leprosy is a potentially debilitating chronic infectious disease that can result in permanent nerve damage and deformities,[1] and has been associated with a greater risk of comorbidities such as diabetes.[2] Although current prevalence rates of the disease are low worldwide, with less than 184 238 cases reported globally in 2018,[3] leprosy continues to emerge outside its endemic regions of Southeast Asia, Africa, and Latin America,[4] due to migration.[5] In light of the World Health Organization (WHO)'s goal of reducing leprosy-associated disabilities among new pediatric cases to 0, and reducing the overall occurrence of leprosy-associated grade-2 disabilities to less than 1 case per 1 million people by 2020,[3,6] there is an ongoing need to evaluate the efficacy of treatment options for leprosy.[7]

Caused by the bacterium *Mycobacterium leprae*, the disease results in skin lesions with varying levels of peripheral nerve involvement, and has a wide and complex clinical spectrum, ranging from polar paucibacillary (PB) to multibacillary (MB) leprosy, also referred to as tuberculoid and lepromatous

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leprosy, respectively. As immune-mediated responses to *M. leprae,* termed "reactions," can lead to significant nerve damage, the early and effective treatment of leprosy is crucial for the prevention of permanent nerve damage and deformities.[1]

The WHO currently recommends a 12-month course of multidrug therapy (MDT) containing rifampin, clofazimine, and dapsone for the treatment of MB leprosy[8]; however, the prolonged duration of therapy necessitated by standard WHO MDT poses barriers to treatment adherence,[9-12] and clofazimine-associated skin pigmentation (occurring in 100% of patients [$n = 21$ in a study by Maia et al)[13] contributes to leprosy-associated stigma, acting as a further treatment deterrent.[14] In addition, clofazimine's tolerability is limited by a high occurrence of function-limiting pruritus, and can also be associated with gastrointestinal side effects including nausea, vomiting, and abdominal pain.[15] In rare cases, clofazimine has been associated with severe enteropathy and splenic infarcts.[15,16] Lastly, concerning the use of clofazimine-containing regimens, it should be noted that the 2018 WHO recommendation to treat PB leprosy with the 3-drug combination of rifampin, dapsone, and clofazimine (rather than the previously used 2-drug combination of rifampin and dapsone only) has recently been shown to be limited by low-quality evidence and may be challenging to justify in light of clofazimine-associated adverse events.[14]

A further consideration in the treatment of leprosy, in the case of dapsone-containing MDT, is the rare but potentially fatal occurrence of dapsone hypersensitivity syndrome (DHS). As no risk-stratification guidelines for DHS exist, care must be taken to ensure the early identification of the clinical presentation of DHS and subsequent discontinuation of dapsone.[17,18]

In addition to nonadherence, risk of relapse remains a concern associated with standard MDT. Although several studies demonstrate low relapse rates after standard MDT treatment,[19] others report relapse rates as high as 6.6%.[20] Moreover, based on time intervals of recurrence, studies have speculated that some relapses may be due to the persistence of infectious agents in the host, rather than to new infections, suggesting that standard MDT may not be fully effective in clearing mycobacteria.[20,21] As such, there is an urgent need to identify and evaluate shorter, more effective, and well-tolerated treatment options.[22]

The fluoroquinolone ofloxacin is a promising component of new MDT regimens due to its high bactericidal activity.[22,23] In a phase III clinical trial, a 4-week course of ofloxacin was found to reduce viable *M. leprae* bacteria by 99.99%[24]; however, further studies are needed to more comprehensively evaluate the efficacy of ofloxacin-containing MDTs (OMDTs) for the treatment of leprosy.[25] Although several studies report similarly low treatment failure rates,[26] similar rates of bacterial clearance after onset of treatment,[10,27] and similar improvements in skin lesions,[10] for OMDTs compared to standard WHO MDT, other studies have attributed adverse side effects (including insomnia, nausea, and headaches) to ofloxacin.[13] Moreover, further studies have concluded that single-dose rifampin, ofloxacin, and minocycline (ROM) therapy is less effective than MDT for the treatment of PB leprosy, whilst the comparison of the efficacy of multi-dose ROM and standard MDT in the case of MB leprosy remained inconclusive.[28] Limitations of the existing literature evaluating the effectiveness of OMDTs therefore include that multi-dose ROM therapy has been understudied, as has the effectiveness of OMDTs in the case of MB as opposed to PB leprosy.

Investigation of whether the treatment regimen has an effect on the incidence of reactions is also important, as previous such analyses have yielded conflicting results, with 1 reporting a higher occurrence of reactions in patients on ROM, whilst others reporting similar incidences of reactions compared to standard MDT, although small sample sizes were also cited in these studies as a significant limitation of their validity.[28] Finally, as a fluoroquinolone antibiotic, clinicians must be cognizant of adverse drug effects including tendinopathy and tendon rupture, peripheral neuropathy, antibiotic-associated diarrhea, and C. *difficile* colitis. Further serious but rare side effects include aortic aneurysms and dissections, with a recent study showing increased hazards among patients on fluoroquinolones compared to amoxicillin.[29] The potential for occurrence of long-term disabling side effects due to fluoroquinolones has also been highlighted in recent years.[30] Overall, both ofloxacin and clofazimine have side effects that should be taken into consideration along with patients' preferences and clinical characteristics when determining the most appropriate treatment. Considering the limitations in the literature surrounding the efficacy of OMDTs, we aimed to evaluate treatment efficacy, safety, and adherence among patients receiving OMDT for MB and PB leprosy in our ambulatory tropical medicine clinic in Toronto, Canada.

Methods

Study Design and Data Collection

The aim of the study was to evaluate treatment efficacy, safety, and adherence among patients receiving OMDT for MB and PB leprosy in an ambulatory tropical medicine clinic. We retrospectively identified all patients treated for leprosy at our center over an 8-year time period (2011-2019). Patient data were extracted from electronic patient records and medical charts using a validated clinical safety tool, evaluated in a previous study.[31] This standardized form includes patient information pertaining to demographics, clinical presentation, treatment course, laboratory and microbiological investigations, treatment outcomes, and adverse events. At our clinic, standard prescribing practices for leprosy treatment include rifampin, dapsone, and ofloxacin (RDO) MDT, taken daily for approximately 1 year as the first-line treatment, whilst monthly ROM may be administered to high bacillary load MB patients to complete 2 years of therapy following the year of daily OMDT,

and to PB patients who are unable to take 6 months of daily rifampin and dapsone.[32] Both the study protocol and the data collection form were approved by the University Health Network Research Ethics Board and Institutional Review Board.

Outcomes

Primary outcomes of the evaluation of OMDT were categorized as follows: treatment effectiveness, treatment safety, and treatment adherence. As a reduction in active skin lesions is the most relevant indicator of treatment efficacy, the proportion of patients who clinically resolved at the completion of treatment was used as a marker of treatment efficacy. For patients who had a high initial bacillary load (BI ≥4 +) and a complex clinical course (characterized, for example, by frequent treatment interruptions), slit-skin smears were done at relevant intervals in order to assess changes in bacillary index, reductions in which are also indicative of treatment efficacy. However, as the slit-skin smear procedure is invasive, time consuming, and painful, few patients received both baseline and follow-up slit-skin smears ($n = 2$), and clinical improvement was therefore the primary indicator of OMDT efficacy in this analysis. Bacterial indices were measured as per standard on a logarithmic scale, from 0 to 6+, and an outcome of 100-fold reduction was measured. A decrease in BI from 3 + to 1+, for example, would indicate a 100-fold reduction in the number of bacilli observed per microscopic field.

Treatment safety was evaluated clinically based on the occurrence of erythema nodosum leprosum (ENL) or type 1 reactions; adverse drug effects known to occur with fluoroquinolones (eg, allergy, tendinopathy, *C. difficile* colitis); and cessation of treatment due to subjective or objective evidence of adverse drug reactions (eg, biochemical hepatitis). Peripheral neuropathy was not categorized as a marker of safety and tolerability due to the universal baseline peripheral neuropathy associated with our leprosy patients, many of whom have had years-long delays to diagnosis.[1] Treatment safety was also evaluated biochemically and hematologically according to routine laboratory investigations. Methemoglobin levels were monitored in patients on dapsone, and random glucose levels along with urinalysis and hemoglobin A1c were monitored particularly in patients who were on prednisone and thus at potential risk for steroid-induced hyperglycemia and diabetes. In addition, liver function was monitored for all patients on rifampin-containing regimens, other than in those who received single-dose ROM for single-lesion PB leprosy.

Finally, treatment adherence was assessed based on the total number of treatment interruptions of any length, and total loss to follow-up.

Statistical Analysis

Descriptive statistics (mean [SD], median [range], or proportions) are provided for demographic and outcome variables. Data were stratified according to age, sex, clinical spectrum, and treatment regimen. Univariate analyses of the effect of these factors on treatment outcomes were conducted through calculation of prevalence ratios (PR). Given the small sample size, differences between categorical outcomes were compared using Fisher's exact test. Hypothesis tests were 2-sided. Analyses were conducted in R version 3.6.2.

Results

Patient Demographics, Clinical Presentation, and Treatment

Twenty-six patients receiving OMDT were included in the study. Thirteen (50%) were female, and the median age of the sample was 49.5 years (range: 3-94 years). Nineteen patients (73%) presented with MB leprosy, including 6 (23%) with lepromatous leprosy (LL), 4 (15%) with borderline lepromatous leprosy (BL), and 9 (35%) with borderline leprosy (BB). Seven patients (27%) had PB leprosy, including 2 (8%) with borderline tuberculoid leprosy (BT), 3 (12%) with tuberculoid leprosy (TT), and 2 (8%) with indeterminate stage or single-lesion PB leprosy (Table 1).

Twenty patients (77%) received RDO (taken daily) as their initial treatment (18 MB patients and 2 PB patients), for a duration of at least 1 year, although 9 patients (45% of those on RDO) were taken off of dapsone prematurely due to adverse side effects, including 7 patients (35% of those on RDO) with methemoglobinemia. Two patients (8%) with TT received monthly ROM for 6 months, 1 patient (4%) with BL received monthly ROM for 24 months, and 3 patients (12%) received single-dose ROM (with TT: $n = 1$; with single-lesion PB: $n = 2$).

Treatment Effectiveness

At the time of analysis, 23 patients (88%) had completed their course of treatment, and all were clinically cured (on R DO: $n = 18$, on single-dose ROM: $n = 3$, on monthly ROM × 6 months: $n = 2$). No patients were lost to follow-up prior to completing treatment; however, 5 PB patients (19%) were lost to long-term follow-up, and 3 (12%) were still on treatment (Table 2). Of the 2 patients who received both baseline and follow-up slit-skin smear analyses, both showed a 100-10 000-fold reduction in bacillary load (from 5+ to 1+ [ear], 3+ to 1+ [arm] [$n = 1$ over a period of 22 months, and 4+ to 1+ [elbow] over a period of 27 months [$n = 1$]; Table 2).

Leprosy Reactions

Eighteen patients (69%) experienced either ENL ($n = 7$, 27%), type 1 reactions ($n = 7$, 27%), or both (n = 4, 15%). No patients stopped ofloxacin due to adverse drug effects, and there were no cases of allergic hypersensitivity, tendinopathy, or *C. difficile* colitis (Tables 2 and 3). All but 1 of the

Table 1. Patient Demographic and Clinical Characteristics by Treatment.

Patient characteristics *n* (%) unless otherwise indicated	All patients (*n* = 26)	RDO (*n* = 20)	ROM (*n* = 6)
Age, years, median (IQR)	49.5 (32.3, 65.8)	52.0 (36.0, 66.8)	14.5 (7.0, 53.5)
Age >65	7 (27)	5 (25)	2 (33)
Male	13 (50)	10 (50)	3 (50)
Clinical spectrum:			
LL	6 (23)	6 (30)	0 (0)
BL	4 (15)	3 (15)	1 (17)
BB	9 (35)	9 (45)	0 (0)
BT	2 (8)	2 (10)	0 (0)
TT	3 (12)	0 (0)	3 (50)
IS	2 (8)	0 (0)	2 (33)

Abbreviations: BB, mid-borderline leprosy; BL, borderline lepromatous leprosy; BT, borderline tuberculoid leprosy; IQR, interquartile range; IS, indeterminate stage/single-lesion paucibacillary leprosy; LL, lepromatous leprosy; RDO, rifampin, dapsone, ofloxacin; ROM, rifampin, ofloxacin, minocycline; TT, tuberculoid leprosy.

patients experiencing a reaction received prednisone, with 1 requiring only nonsteroidal anti-inflammatory medications for symptom control, and 2 (8%) also received thalidomide.

Although there was a higher prevalence of both ENL and type 1 reactions among patients with MB disease compared to those with PB disease, both confidence intervals include the null (ENL: PR = 9.20, 95% CI = 0.61-138.29, P = .010; type 1: PR = 3.68, 95% CI = 0.57-23.76, P = .178). Furthermore, male patients were more likely than female patients to experience ENL reactions but not type 1 reactions, although this difference was not statistically significant in either case (ENL: PR = 2.67, 95% CI = 0.90-7.86, P = .111, type 1: PR = .57, 95% CI = 0.22-1.49, P = .428).

Patients over 65 years of age were not more likely to experience ENL reactions than younger patients (PR = 1.02, 95% CI = 0.37-2.78, P = 1.000). Similarly, the prevalence of type 1 reactions was no different in patients older than 65 years compared to those aged 65 or under (PR = 1.55, 95% CI = 0.65-3.70, P = .407).

The prevalence of ENL reactions was not higher in those patients receiving daily RDO compared to those receiving monthly ROM (PR = 3.00, 95% CI = 0.48-18.93, P = .197). The prevalence of type 1 reactions appeared to be higher in those receiving RDO; however, the confidence interval for the PR is wide and includes the null (PR = 7.67, 95% CI = 0.52-113.98, P = .024; Table 3).

Table 2. Treatment Outcomes and Adverse Events.

Outcomes	*n* (%) (*N* = 26)[a]
Clinical cure[b]	
Clinical resolution	23 (88)
Unresolved (ongoing treatment)	3 (12)
Fold reduction in bacterial index[c] (*n* = 2)	
100-10 000	2 (100)
Patients experiencing reactions	
Type 1	7 (27)
ENL	7 (27)
Both	4 (15)
Any reaction	18 (69)
Glucose levels above normal[d]	
Of those on steroids (*n* = 17)	8 (47)
Of those not on steroids (*n* = 9)	1 (11)
Total	9 (35)
Referred to diabetes care	8 (31)

Abbreviation: ENL, erythema nodosum leprosum.
[a]Unless otherwise indicated.
[b]All patients who completed treatment experienced clinical resolution.
[c]Bacterial indices are measured on a logarithmic scale, from 0 to 6+. Therefore, a decrease in BI from 3+ to 1+, for example, would indicate a 100-fold reduction in the number of bacilli observed per microscopic field.
[d]Threshold (glucose above normal): >8.0 mmol/L.

Treatment Adherence

Treatment adherence and interruptions are described in Table 4. To date, 15 patients (58%) experienced no treatment interruptions, and 9 patients (35%) experienced at least 1 treatment interruption due to adverse side effects, all of which were attributable to the dapsone component of their MDT. Two patients (8%) were nonadherent to treatment at least once, due to having misunderstood instructions regarding when to take the medication. Seven patients (27%) were lost to follow-up, 3 of which had completed their treatment at time of loss to follow-up.

Table 3. Prevalence Ratios for Occurrence of Reactions, Stratified by Clinical and Demographic Characteristics.

	Type of reaction					
Demographic characteristics	ENL *n* (%)[a]	PR (95% CI)	*P* value[b]	Type 1 *n* (%)[a]	PR (95% CI)	*P* value[b]
Age						
>65 (n = 7)		1.02	1.000	4 (57)	1.55	.407
≤65 (n = 19)		(0.37, 2.78)		7 (37)	(0.65, 3.70)	
Sex						
Male (*n* = 13)	8 (62)	2.67	.111	4 (31)	0.57	.428
Female (*n* = 13)	3 (23)	(0.90, 7.86)		7 (54)	(0.22, 1.49)	
Clinical spectrum						
MB (*n* = 19)	11 (58)	9.20	.010	10 (53)	3.68	.178
PB (*n* = 7)	0 (0)	(0.61, 138.29)		1 (14)	(0.57, 23.76)	
Treatment type						
RDO (*n* = 20)	10 (50)	3.00	.197	11 (55)	7.67	.024
ROM (*n* = 6)	1 (17)	(0.48, 18.93)		0 (0)	(0.52, 113.98)	

Abbreviations: CI, confidence interval; ENL, erythema nodosum leprosum; MB, multibacillary leprosy; PB, paucibacillary leprosy; PR, prevalence ratio; RDO, rifampin, dapsone, ofloxacin; ROM, rifampin, ofloxacin, minocycline.
[a]% by row subgroup.
[b]Fisher's exact *P* value.

Adverse Events

No patient on OMDT discontinued treatment due to an ofloxacin-related adverse event. There were no occurrences of allergic reaction, tendinopathy/tendon rupture, or *C. difficile* colitis in those receiving OMDT.

Discussion

Standard MDT for leprosy is limited by the long duration of therapy and substantial adverse effects associated with the clofazimine component. Although ofloxacin-based MDT is of similar duration, the fluoroquinolone component offers the possibility of improved tolerability, though data accrued in nonendemic areas are lacking. In this small case series of leprosy outside of an endemic area, we have demonstrated both a high cure rate and tolerability of OMDT regimens. The cure rate observed herein is similar to those of other studies evaluating monthly ROM and standard WHO MDT, with 1 randomized controlled trial (RCT) reporting a 2-year cure rate of 93.1%, for ROM,[33] and another RCT reporting 2-year cure rates of 97.0% and 99.0% for WHO MDT and monthly ROM, respectively.[34] In 58 patients who received an ofloxacin-containing regimen and followed for an average of 10.8 years as part of a clinical trial, only one relapse was noted at 3-years post-treatment.[35] This high cure rate suggests the viability of OMDT as an alternative to standard WHO MDT, which is particularly limited by stigmatizing hyperpigmentation due to the clofazimine component.

As mentioned, ofloxacin is a typically well-tolerated component of alternative MDT for leprosy. Previous studies corroborate our observation of few side effects due to the ofloxacin component of the OMDTs.[10,36] One study has previously reported mild gastrointestinal symptoms attributable to ofloxacin,[13] but none have documented serious adverse events such as complicated *C. difficile* colitis, Achilles tendon rupture, or serious hypersensitivity reactions.

Table 4. Treatment Completion, Interruption, and Attrition.

Treatment adherence	Number of patients (%)
Patient nonadherence[a]	2 (8)
At least 1 treatment interruption due to adverse side effects:	9 (35)
Methemoglobinemia	7 (27)
Fever or reporting generally feeling unwell	2 (8)
Full adherence to initial treatment to date[b]	15 (58)

[a]Patient discontinued treatment prior to end of treatment course, and without first reporting adverse side effects to physician (in the above cases due to misunderstanding instructions for taking treatment).
[b]No treatment interruptions since beginning of first treatment.

The risk of leprosy reactions is an important consideration when selecting MDT regimens. In our experience of leprosy management in a nonendemic setting over a 20-year period, leprosy reactions occurred in approximately 25% of patients started on MDT, which in most cases was standard WHO MDT.[1] Studies evaluating OMDTs have reported reactions ranging from 14.8%[37] to 33.3% of patients,[38] which is much lower than our observation of 69% experiencing ENL or type 1 reactions in this small series. It should be noted however that this includes 11 patients (42%) who were in reaction at presentation. Our findings may simply reflect a greater tendency toward reaction in those in the borderline to borderline-lepromatous range of the clinical spectrum, which tends to account for a large number of our patients as previously described.[1] One study evaluating standard WHO MDT reported a reaction rate of 54.9%,[39] whilst another reported 27% and 8% of patients experiencing reactions on 12-month and 24-month courses of standard WHO MDT, respectively.[40] A smaller study similar to our own compared 10 patients on ROM to 11 patients on standard WHO MDT and reported leprosy reactions in 70% and 63.6% of patients, respectively.[10] Thus, the reporting of reactions in the literature is highly variable, and dependent on many competing factors, not the least of which being how authors defined and classified reactions, the geographic location of the study, the clinical spectrum of enrollees, and the duration of treatment and follow-up. The rate of reactions observed in our small series is comparable to that in other small studies of OMDT; however, the reported variability highlights the need for both larger prospective studies of OMDT and a clear WHO MDT control group.

Recognizing the psychosocial aspects of leprosy is especially important to its management, and these aspects would include the high degree of associated social stigma,[41] the probable socioeconomic marginalization due to recent migration status, and cultural and language barriers to treatment adherence and care seeking. While many of these challenges and barriers require systems-level interventions to overcome, reducing social stigma by eliminating the classic hyperpigmentation of clofazimine treatment is a low-cost, low-tech intervention that is likely to improve treatment adherence and patient well-being. The fact that substitution of ofloxacin for clofazimine appears equally efficacious in trials, makes such a psychosocial intervention even more palatable.

In this series, 19% of patients were lost to long-term follow-up after completion of OMDT, all of whom had PB disease, and most of whom were treated with single-dose ROM for single-lesion PB leprosy. Studies of standard MDT report even higher loss to follow-up rates, with 1 study reporting a 50% and 60% loss to follow-up among patients living closer to and further from the treatment clinic, respectively.[11] A further study investigating treatment default among patients receiving ROM compared to standard WHO MDT reported significantly lower default rates for ROM of 14.8% and 9.1% for PB and MB leprosy, respectively, compared to standard MDT where default rates were 28.8% and 34.5% for PB and MB leprosy, respectively.[42] Our findings underscore the continued need to address treatment attrition and loss to follow-up, and to prospectively and rigorously investigate strategies to encourage long-term patient retention.

Limitations and Areas for Further Research

This was a small observational study, with a sample size that reflects usual referral volumes for leprosy in our center. A primary limitation of the study was the absence of a nonofloxacin control group, which would be required for a quantitative rather than primarily descriptive evaluation of OMDT in our setting. As previously mentioned, accrual of further data in a prospective nonobservational manner is warranted.

Given the small sample size, further analytic methods such as logistic regression to allow adjustment for relevant covariates such as sex and age were not possible, and thus only unadjusted estimates could be presented. As only univariate analyses were possible, our results are subject to potential confounding factors, including differences in clinical spectrum, demographic characteristics, and comorbidities among patients. Our observation that patients on RDO may have been more likely to experience reactions than those on ROM may simply reflect the clinical spectrum of the patients, recognizing that reactions are known to occur more often in MB patients,[8] while the ROM group would have included patients with single-lesion PB leprosy. Therefore, recognizing the complex clinical manifestations of leprosy, and the presence of multiple demographic and clinical co-variables, larger studies are urgently needed in order to facilitate a multivariate analysis that adjusts for confounding factors to more precisely evaluate the efficacy and safety of OMDT.

Conclusions

Overall, our small series demonstrates that OMDT is both safe and effective, reporting similar cure rates to prior studies of OMDT,[33-35] and comparing favorably to standard MDT. Moreover, we demonstrate in our small series that OMDT eliminates some of the adherence barriers associated with standard MDT, particularly the stigmatizing clofazimine-related side effects.[14] Despite this, further RCTs would be beneficial, to provide a stronger evidence base for the relative efficacy of OMDT compared to routine treatment. OMDT therefore represents a practical treatment alternative to standard WHO MDT for the treatment of leprosy in nonendemic areas.

Declaration of Conflicting Interests

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