Novel approaches in the treatment of Hansen’s disease (Leprosy): a case series of multidrug therapy of monthly rifampin, moxifloxacin, and minocycline (RMM) in the United States

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Abstract: The World Health Organization (WHO) recommends multidrug therapy (MDT) for the treatment of paucibacillary and multibacillary forms of leprosy, also known as Hansen’s disease (HD). MDT combinations of dapsone, rifampin, and clofazimine have reduced the prevalence of the disease but are not without adverse effects impacting regimen adherence. Hence, an urgent need exists to consider alternative MDT regimens with an improved safety profile that promotes treatment adherence. Herein, we described a case series of 10 patients with HD (nine patients with multibacillary leprosy and one with pure neural leprosy) treated with monthly rifampin, moxifloxacin, and minocycline (RMM). The United States National Hansen’s Disease Program (NHDP) diagnosed and treated patients across US institutions. All patients received a regimen of 12–24 months of RMM. We reviewed the clinical outcomes, adherence, rate of completion, and adverse events of patients treated with monthly RMM from January 2019 to August 2022. Nine patients had multibacillary leprosy, with some having type-2 reactions. One patient had pure neural leprosy with a reversal reaction. In this case series, we identified that all patients completed the RMM regimen without treatment interruptions. None of the patients experienced any skin hyperpigmentation or any significant side effects. All patients tolerated the monthly RMM regimen with rapid improvement of skin lesions and without logistic hurdles. Based on previous clinical evidence and the results of this case series, the NHDP and other programs should consider the RMM regimen as first-line therapy.

Keywords: clofazimine, Hansen’s disease, leprosy, methotrexate, moxifloxacin, multidrug therapy, prednisone, rifampin

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Introduction
By 2000, the World Health Organization (WHO) declared leprosy, also known as Hansen’s disease (HD), eliminated as a public health threat.1 Despite this declaration, to this day, leprosy remains a significant cause of neurologic dysfunction and disability, with more than 4 million new cases identified from 2000 to 2020.2 In 2021, the WHO reported 127,396 new cases globally, the lowest ever reported new cases, but this decrease

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obeys the underreporting and underperformance of national leprosy programs imposed by the restrictions of the COVID-19 pandemic. In the United States, approximately 200–300 new cases are reported annually to the United States National Hansen’s Disease Program (NHDP) in Baton Rouge, Louisiana.

Since 1985, the WHO has recommended multidrug therapy (MDT) consisting of rifampin, clofazimine, and dapsone as the mainstay of therapy for HD. The WHO recommends daily self-administered dapsone and clofazimine for multibacillary forms of leprosy and monthly supervised rifampin and clofazimine. The US NHDP follows WHO-recommended regimen with MDT modification, including the use of daily rifampin. The duration of therapy depends on clinical and histopathologic improvement. Despite its proven efficacy, MDT has significant limitations, including drug toxicity and operational challenges. The high total pill burden leads to lower adherence and subsequent negative impact on the quality of life of those affected with HD. Dapsone is associated with rare but life-threatening toxicities, including hemolytic anemia, exfoliative dermatitis, and hypersensitivity reactions. Furthermore, dapsone is not favored by many experienced leprologists due to its bacteriostatic action against Mycobacterium leprae. Clofazimine can cause skin discoloration, which tends to localize in plaques and nodules on the face and extremities leading to stigmatizing aesthetic abnormalities. Clofazimine-induced pigmentation takes months to years to resolve after discontinuation of the drug (Figure 1). In addition, daily rifampin may cause serious drug–drug interactions reduced glucocorticoid efficacy, hepatotoxicity, acute interstitial nephritis, and other systemic side effects.

Many experts have advocated using alternative antimicrobial drug regimens with reduced toxicity. In this regard, administering single-dose therapy with rifampin, ofloxacin, and minocycline (ROM) for single lesion paucibacillary leprosy is safe and effective. In addition, monthly ROM therapy has been advocated for patients unable to take first-line MDT for borderline and lepromatous forms of leprosy (multibacillary). In many settings, moxifloxacin may substitute ofloxacin as it is a more widely available fluoroquinolone with significant microbicidal activity. Due to its longer half-life, rifapentine has been substituted for rifampin, wherein the combination of rifampin, moxifloxacin, and minocycline (RMM) is microbicidal, and the kinetics supports its clinical use.

Over the years, the NHDP has documented multiple cases of patients who received MDT who developed clofazimine-induced pigmentation. In response to these challenges and based on recent reports demonstrating safety and efficacy data, the NHDP began recommending monthly RMM for 12–24 months to all patients.
patients with newly diagnosed disease. Herein, we described a case series of 10 patients (nine patients with multibacillary leprosy and one with pure neural leprosy) treated with RMM.

**Methods**

We retrospectively assessed a monthly drug regimen of RMM in treating multibacillary forms of leprosy and in pure neural leprosy. We included patients with a new confirmed diagnosis of HD by microbiologic, histologic, and clinical features. We collected demographic and clinical information from all patients to describe their clinical response to this multidrug regimen: adverse events during treatment, adverse events at the time of treatment completion, and clinical outcomes. Each medical provider determined the frequency of follow-up evaluations at his or her discretion. The main objective of this case series is to document the safety and efficacy of RMM. The secondary objectives were to define the clinical, bacteriologic, and histologic outcomes in patients we treated through the NHDP. In the United States, the NHDP coordinates the medical care and provides medications for any patient diagnosed with HD in US territories. The coordination of care is through providers in collaboration with the Chief Medical Officer (BS) of the NHDP. This program distributed medications to providers or directly to patients in blister packs, including monthly antimicrobial therapy consisting of rifampin 600 mg, minocycline 100 mg, and moxifloxacin 400 mg for 12–24 months. Blister packs also included folic acid and vitamin D. All patients were assessed for immunological reactions at the time of entrance to care. Patients identified as having immunological reactions [type 1 or reversal reaction or type 2 or erythema nodosum leprosum (ENL)] received along with RMM, low-dose weekly methotrexate (MTX) 7.5–15 mg weekly ± low-dose prednisone 2.5–10 mg/day. Two patients with ENL required additional therapy with thalidomide. Medical providers at each institution individualized tapering of immunomodulating medications. Our study did not require an ethical board approval because it is not considered research, and it is limited to description of clinical features and treatment outcomes. The NHDP obtained written consent from patients for publication. Patients who were treated by individual practitioners with overseen by the NHDP provided written and/or verbal consent for publication.

**Case series description**

In collaboration with the US NHDP, providers in multiple health settings across the United States provided treatment to 10 patients with a monthly MDT containing RMM as well as immunomodulatory therapy in those with immunological reactions. We retrospectively reviewed their medical records to identify toxicities and laboratory abnormalities and detect any treatment interruptions due to adverse events (Table 1). Five patients received a 12-month regimen of self-administered treatment every 4 weeks, and six completed a 24-month course. There were nine men and one female with a median age of 45 (17–77 years). All providers reported consistent and rapid clearance of skin lesions with definite clinical improvement observed (Figures 2–4). There were only minor gastrointestinal side effects in 2 of the 10 (20%) patients with the use of monthly RMM. There were no reports of major adverse events, with only one patient developing mild elevation of transaminases that returned to normal levels within 4 weeks despite the continuation of MDT. We identified no other drug toxicities or laboratory abnormalities during the treatment course of all patients (Tables 1 and 2).

**Discussion**

We successfully treated 10 patients with HD with monthly use of MDT RMM. All patients finished 12–24 months of the regimen with satisfactory clinical outcomes, and not one patient stopped therapy because of side effects.

Despite the success of MDT in reducing the prevalence of HD, there is an urgent need for alternative drug regimens that exhibit clinical efficacy without the adverse side effects and resultant noncompliance. Indeed, one of the many setbacks when instituting the WHO MDT is poor adherence to daily doses of the medications. The introduction of clofazimine into MDT to treat HD relies on the assumption that it reduces the risk of ENL in patients with multibacillary disease. However, until today, there is no concrete evidence for this treatment. Furthermore, clofazimine is associated with skin discoloration or ichthyosis in most patients, and approximately 30% of patients report gastrointestinal side effects with clofazimine. A recent systematic review and a meta-analysis evaluated the efficacy of single-dose ROM
| Type of leprosy                  | Age/gender | Treatment regimen and duration | Leprosy reaction | Immune modulation therapy | Outcome                                                                 | Adverse events                          |
|---------------------------------|------------|--------------------------------|------------------|---------------------------|--------------------------------------------------------------------------|------------------------------------------|
| Borderline (multibacillary)     | 70/male    | Rifampin Minocycline Moxifloxacin (12 months) | Reversal reaction | Low-dose prednisone methotrexate | Completed therapy: rapid resolution of skin lesions and no skin discoloration | None                                     |
| Lepromatous (Multibacillary)    | 20/male    | Rifampin Minocycline Moxifloxacin (24 months) | ENL              | Low-dose prednisone methotrexate | Completed therapy: rapid resolution of skin lesions and no skin discoloration | Mild elevational Liver enzymes that resolved |
| Borderline Lepromatous (Multibacillary) | 27/male | Rifampin Minocycline Moxifloxacin (24 months) | ENL              | Low-dose prednisone methotrexate | Completed therapy: rapid resolution of skin lesions and no skin discoloration | None                                     |
| Lepromatous (Multibacillary)    | 36/male    | Rifampin Minocycline Moxifloxacin (12 months) | ENL              | Methotrexate Thalidomide   | Completed therapy: rapid resolution of skin lesions and no skin discoloration | Mild GI                                  |
| Borderline Lepromatous (Multibacillary) | 77/male | Rifampin Minocycline Moxifloxacin (24 months) | ENL and reversal reaction | Low-dose prednisone methotrexate | Completed therapy: rapid resolution of skin lesions and no skin discoloration | Mild GI                                  |
| Lepromatous (Multibacillary)    | 72/female  | Rifampin Minocycline Moxifloxacin (12-months) | ENL              | Low-dose prednisone methotrexate | Completed therapy: rapid resolution of skin lesions and no skin discoloration | None                                     |
| Lepromatous (Multibacillary)    | 37/male    | Rifampin Minocycline Moxifloxacin (24 months) | ENL              | Low-dose prednisone methotrexate | Completed Therapy: rapid resolution of skin lesions and no skin disoloration | None                                     |
| Lepromatous (Multibacillary)    | 17/male    | Rifampin Minocycline Moxifloxacin (24-months) | ENL              | Low-dose prednisone methotrexate thalidomide | Completed therapy: rapid resolution of skin lesions and no skin discoloration | None                                     |
| Lepromatous (Multibacillary)    | 39         | Rifampin Minocycline Moxifloxacin (12 months) | ENL              | Methotrexate              | Completed therapy: rapid resolution of skin lesions and no skin discoloration | None                                     |
| Pure Neural Leprosy (Paucibacillary) | 70         | Rifampin Minocycline Moxifloxacin (12 months) | Reversal reaction | Low-dose prednisone methotrexate | Completed therapy: rapid resolution of skin lesions and no skin discoloration | None                                     |

ENL, erythema nodosum leprosum; GI, gastrointestinal side effects.
therapy in treating paucibacillary and multibacillary leprosy patients. This study demonstrated that single-dose ROM therapy was less effective than MDT in paucibacillary patients but effective in treating single-lesion paucibacillary forms. However, a randomized study conducted by Kumar et al. in Agra District in India in 2015 showed that MDT with ROM for 6 months was comparable to a 6-month MDT with standard WHO therapy (daily dapsone and monthly directly observed dose of rifampin) with similar acceptability, cure rate, and relapse rate.

Figure 2. A 20-year-old male with multibacillary Hansen’s disease (nodular lepromatous) treated with monthly rifampin, minocycline, and moxifloxacin and demonstrated rapid clinical improvement of skin nodules and plaques. This patient completed a 24-month course of monthly ROM with adequate adherence to the regimen and no adverse events without evidence of skin lesions or hyperpigmentation.

Figure 3. A 72-year-old female with multibacillary Hansen’s disease (nodular lepromatous) treated with monthly rifampin, minocycline, and moxifloxacin, and demonstrated clinical improvement in the size and appearance of the plaques. This patient completed a 12-month ROM with adequate adherence to the regimen and no adverse events without evidence of skin lesions or hyperpigmentation.
Figure 4. A 70-year-old male with multibacillary Hansen’s disease (borderline lepromatous leprosy) treated with rifampin, minocycline, and moxifloxacin demonstrating substantial improvement after 24 months of therapy.

Table 2. Comparison of the traditional first-line therapy versus monthly therapy.

|                                     | Daily standard WHO-recommended multidrug therapy | Monthly-therapy using RMM |
|-------------------------------------|------------------------------------------------|--------------------------|
| Clinical outcomes                   | Proven clinical efficacy                         | Rapid clinical response likely driven by low frequency of side effects of multidrug therapy |
| Side effect profile                 | High frequency of side effects including cosmetic| Minimal                  |
| Quality of life                     | High burden of pills                             | Patients are happy because of rapid clinical response with low burden of pills and minimal side effect profile |
|                                    | Frequent side effects                             |                          |
|                                    | Some improvement in overall markers of QOL        |                          |
| Adherence to medications and completion of therapy | Reduced adherence to multidrug therapy       | Low pill burden and safety profile improve adherence |

QOL, quality of life; RMM, rifampin, moxifloxacin, and minocyclin; WHO, World Health Organization.
Two clinical studies evaluated MDT ROM for multibacillary leprosy. A study in the Philippines compared 21 patients with borderline leprosy and lepromatous leprosy who received either monthly ROM for 24 months or standard multibacillary MDT (monthly rifampin with daily dapsone and clofazimine). Both groups had comparable reductions in bacterial index scores (BI), clinical improvement in skin lesions, and histological appearance of their skin biopsies. Moreover, the BI continued to fall after the completion of anti-biotic treatment in those who received ROM, and no evidence of relapses during the subsequent 64 months. All patients who were on the WHO-MDT developed clofazimine-induced pigmentation. No toxicities occurred in patients receiving ROM. A second study conducted in Brazil with a similar study design in patients with borderline lepromatous and lepromatous leprosy demonstrated a similar fall in BI and similar clinical and histological improvements after 24 months of treatment with either WHO-MDT or ROM. However, patients who received clofazimine experienced skin discoloration.

Recent studies support the safety and microbicidal activity of monthly doses of RMM antibacterial drugs. Studies using post-exposure prophylaxis regimens have shown that kinetic mouse footpad screening assays demonstrate that intermittent monthly antibacterial therapy with RMM delays discernable \textit{M. leprae} growth. These data demonstrates the high efficacy of MDT with improved drug combinations in both early and late infection. Moxifloxacin has robust bactericidal activity in treating patients with multibacillary leprosy with rapid clearance of skin lesions and definite clinical improvement observed with mild side effects, toxicities, and laboratory abnormalities. In addition, discontinuation of therapy has not been reported with monthly moxifloxacin when added to rifampin and dapsone.

Bactericidal pulse therapy using the combination of RMM is a drug combination that improves adherence and provides operational advantages such as observation of its virtually observed administration or self-administration with minimal instructions. Moreover, monthly RMM reduces the chances of severe adverse events frequently associated with dapsone or clofazimine. The use of RMM has additional benefits for patients. Many of the patients seen with HD in the United States are working-age adults with long work hours and family responsibilities that may impact their availability to attend clinic visits and ultimate adherence to complicated drug regimens. Many have co-morbidities that predispose them to have potential drug–drug interactions when receiving daily rifampin therapy.

Furthermore, because many of our patients have low health literacy levels, blister packs for monthly administered drugs facilitated adherence by

| Table 3. Comparison of benefits of steroid alone versus with combination methotrexate and low-dose prednisone in patients with leprosy reactions. |
|---------------------------------------------|
| **High-dose glucocorticoids** | **Low-dose prednisone and methotrexate*** |
| **Clinical outcomes** | Proven efficacy | Equivalent efficacy leading to better tolerance and accelerating steroid tapering to lower maintenance doses |
| **Side effect profile** | Long term complications of prolonged glucocorticoid therapy including metabolic (hyperglycemia), ocular (cataracts), bone (osteoporosis), and others | Methotrexate used at lower doses and implemented as steroid-sparing regimens provide adequate tolerance with minimal side effect profile |
| **Quality of life** | High burden of pills | Low burden of pills and low incidence of side effects including cosmetic ones |
| **Adherence to medications and completion of therapy** | Reduced adherence to multidrug therapy | Low pill burden and safety profile improves adherence |

QOL, quality of life. *Low-dose methotrexate used at lower doses and implemented as steroid-sparing regimens and administered for shorter periods is safer because never exceed the maximum dosage of 1500 mg when incidence of hepatotoxicity becomes a significant clinical concern.*
simplifying patient instructions. We believe that this strategy partially facilitated the completion of the regimen. A once-monthly drug regimen is revolutionary and successful in achieving higher rates of MDT completion.

In the treatment course of all patients included in this series, we reduced the prednisone dose and added methotrexate as a steroid-sparing agent with great success in treating immunologic reactions. Importantly, the cumulative dose of methotrexate used to treat patients with immunologic reactions does not reach the maximum dose correlating with end-organ damage (liver and lung toxicities) (Table 3). A lower dose of glucocorticoids reduces the risk of many potential long-term sequelae, including metabolic, osteoarticular, and ocular complications. An ongoing randomized, double-blind clinical trial is underway to assess the benefit of a combination of methotrexate and lower doses of prednisolone in treating ENL.

Future randomized clinical trials may add further evidence to using ROM in multibacillary disease. Our study has significant limitations, including a retrospective descriptive design with small sample size, a lack of a control group, and a short follow-up after completion of MDT. However, this observational experience of the clinical effectiveness and safety of RMM contributes to the growing reports of the clinical value of RMM.

In summary, monthly RMM is a favorable and effective alternative treatment for paucibacillary and multibacillary forms of HD. RMM produces rapid clearance of skin lesions and prevents the potential occurrence of life-threatening adverse events associated with dapsone and the stigmatizing skin discoloration of clofazimine. Monthly dosing of moxifloxacin and minocycline reduces the risk of potential adverse events compared with daily therapy. The US NHDP and other national treatment programs need to consider monthly RMM as a first-line multidrug regimen in treating HD.

Declarations

Consent for publication
The National Hansen’s Disease Program (NHDP) obtained written consent for publication from patients monitored by the NHDP. Patients who were treated by individual practitioners overseen by the NHDP provided verbal and/or written consent for publication.

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Pauline A. Hoosepian-Mer: Data curation; Writing – original draft; Writing – review & editing.

Ethics approval and consent to participate
Our study was limited to the description of clinical features and treatment outcomes and therefore did not require ethical board approval.
Barbara Stryjewska: Conceptualization; Data curation; Project administration; Supervision; Writing – original draft; Writing – review & editing.

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Not applicable.

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