Alternative Leprosy Treatment Using Rifampicin Ofloxacin Minocycline (ROM) Regimen – Two Case Reports

Yohanes WIDJAJA, Khairuddin DJAWAD, Saffruddin AMIN, Widyawati DJAMALUDDIN, Dirmawati KADIR, Sri V. MUCHTAR

Department of Dermatology And Venereology, Hasanuddin University Faculty Of Medicine, Makassar, Indonesia

*Correspondence: Khairuddin Djawad, E-mail: duddin@gmail.com

UDC 616.5-002.73-091.8

UDC 616.5-002.73-085

Abstract

Introduction. Leprosy is a disease that predominantly affects the skin and peripheral nerves, resulting in neuropathy and associated long-term consequences, including deformities and disabilities. According to the WHO classification, there are two categories of leprosy, paucibacillary (PB) and multibacillary (MB). The standard treatment for leprosy employs the use of WHO MDT (Multi Drug Treatment) regimen, despite its multiple downsides such as clofazimine-induced pigmentation, dapsone-induced haematological adverse effects, poor compliance due to long therapy duration, drug resistance, and relapse. Multiple studies and case reports using ROM regimen have reported satisfactory results. Nevertheless, there are still insufficient data to elucidate the optimum dosage and duration of ROM regimen as an alternative treatment for leprosy. Previous experience from our institution revealed that ROM regimen given three times weekly resulted in a satisfactory outcome. **Case Reports.** We report two cases of leprosy treated with ROM regimen from our institution. The first case was PB leprosy in a 64-year-old male who presented with a single scaly plaque with erythematous edge on the right popliteal fossa. Sensibility examination showed hypoesthesia with no peripheral nerve enlargement. Histopathological examination confirmed Borderline Tuberculoid leprosy. ROM regimen was started three times weekly for 6 weeks and the patient showed significant clinical improvement at the end of the treatment with no reaction or relapse until after 6 months after treatment. The second case was MB leprosy in a 24-year-old male patient with clawed hand on the 3rd-5th phalanges of the right hand and a hypoesthetic erythematous plaque on the forehead. Histopathology examination confirmed Borderline leprosy. The patients received ROM therapy 3 times a week with significant clinical improvement after 12 weeks. **Conclusion.** ROM regimen given three times weekly for 6 weeks in PB leprosy and 12 weeks in MB leprosy resulted in a significant clinical improvement. Thus, ROM regimen could be a more effective, safer, faster alternative treatment for leprosy.

Key words: Cranial Nerve Diseases; Herpes Zoster Oticus; Neuritis; Signs and Symptoms; Diagnosis; Antiviral Agents; Rare Diseases

Introduction

Leprosy, also known as Hansen's disease, is a chronic disease caused by *Mycobacterium leprae* (*M. leprae*) that primarily affects the skin and peripheral nervous system which may result in neuropathy. The most frightening part of this disease is that it can cause deformity and disability. It can occur to all ages, from an infant to a very old person. Even though the WHO (World Health Organization) attempted to eliminate leprosy in 2000, new cases continued to occur and more than 200,000 new cases of leprosy were reported

in 2016 (1). The transmission of this disease is still poorly understood. It is thought to be transmitted through inhalation of droplets containing *M. leprae* as well as through direct skin contact (1).

In most cases, diagnosis of leprosy can be made by finding one of the three cardinal signs of leprosy: loss of sensation in a hypopigmented or erythematous skin lesion; thickening or enlargement of the peripheral nerve accompanied by loss of sensation and/or muscle weakness in the affected nerve; or positive slit skin smear (1, 2).

Figure 1. (A) Erythematous lesion with hypoesthesia on the right popliteal fossa on day-0, (B) After 6 weeks (day-42) of treatment the erythematous plaque started to fade. (C) Six months after treatment (day-168) the lesion became hyperpigmented with no leprosy reaction or relapse.

Leprosy is classified as paucibacillary (PB) or multibacillary (MB), and the standard treatment for leprosy is MDT (Multi Drug Treatment) regimen recommended by the WHO involving the use of rifampicin and dapsone for 6 months for PB leprosy and rifampicin, clofazimine and dapsone for 12 months for MB leprosy. However, MDT has been linked to multiple downsides such as clofazimine-induced pigmentation, dapsone-induced haematological adverse effects, poor compliance due to long therapy duration, drug resistance, and relapse (1, 3). Thus, an effective alternative regimen with shorter duration and fewer side effects is needed.

In this report, we show a case of PB and MB leprosy, respectively which were successfully treated using ROM regimen three times a week that showed significant clinical improvement with no side effects until after six months of follow-up.

Case Reports

Case Report 1

A 64 year-old man presented with a chief complaint of a single painless and non-itchy erythematous plaque on the right popliteal fossa which had appeared three months before admission. Physical examination revealed erythematous lesion with hypoesthesia without peripheral nerve enlargement. There were no

other lesions on his body. Slit skin smear showed no acid fast bacilli. Histopathology examination showed epidermal atrophy with clear subepidermal zone and abundant granuloma that infiltrated the adnexa and consisting of epithelioid histiocytes with a lot of lymphocytes and datia langhans cell, consistent with borderline tuberculoid (BT) leprosy. Based on clinical examinations, slit skin smear, and histopathological features, BT leprosy was diagnosed. Since the patient refused the MDT regimen, he was prescribed with ROM regimen (Rifampicin 600 mg, Ofloxacin 400 mg, and Minocycline 100 mg) three times weekly for six weeks.

After four weeks of treatment, the erythematous plaque started to fade along with improvement of the hyphoesthesia (**Figure 1a**). At the end of treatment (week 6), the erythematous plaque became flat and faded (**Figure 1b**). The patient himself also reported a subjective, significant improvement of the sensibility that was proven objectively by sensoric examination. There was no leprosy reaction or relapse until after six months after treatment.

Case Report 2

A 24-year-old male patient presented with clawed hand on the 3rd–5th phalanges of the right hand and single hypoesthetic erythematous plaque on the forehead which had ap-

Figure 2. (A) single hypoesthetic erythematous plaque on the forehead with clawed hand on the right hand (day-0). (B) In the 12th week (day-84), the lesion on his forehead disappeared and the patient was able to straighten his finger.

peared 5 months before. There was no pain or pruritus at the lesion. Physical examination revealed hypoesthesia at the lesion and also at the third, fourth, and fifth finger of the right hand with peripheral right ulnar nerve enlargement. Hypotrophy of the tenar and hypotenar muscle was evident and there were no other lesions on his body. Motor tests using voluntary muscle and hand grip tests showed the same strength in both hands.

Slit skin smear showed positive-1 acid fast bacilli. Histopathology examination showed epidermal atrophy with a clear sub-epidermal zone. Epithelioid granulomas surrounded by lymphocytes near adnexa and nerve with no datia langhans cell were found at the dermis. These features were consistent with borderline (BB) leprosy. Based on clinical examinations, slit skin smear, and histopathological features, BT leprosy was diagnosed. Due to the risk of skin pigmentation, the patient refused MDT regimen and was prescribed ROM regimen (Rifampicin 600 mg, Ofloxacin 400 mg, and Minocycline 100 mg) three times weekly for 12 weeks.

After 4 weeks of treatment the erythematous plaque on the forehead started to fade

and an improvement in the sensory and motor test was found. In the 12th week, the lesion on his forehead disappeared and the patient reported significant improvement in sensibility. In addition, the patient was able to straighten his finger. Slit skin smear showed negative acid fast bacilli (**Figure 2**).

Discussion

Until today, the current standard treatment for leprosy remains the MDT regimen that has been recommended by the WHO. This regimen requires not only supervised monthly rifampicin and clofazimine doses but also daily self-administration of dapsone and clofazimine that is related with poor compliance and drug resistance. However, drug resistance, and relapses have been reported (4). The three drugs that comprise MDT have recognized adverse effects. Dapsone, especially in those with glucose-6-phosphate dehydrogenase deficiency, is associated with infrequent but serious toxicities. Clofazimine is associated with generalized skin pigmentation which is the leading cause for MDT refusal. Besides that, long treatment duration leads to low compli-

ance and high drop-out rate (5, 6). Thus, there is still a need to find new alternative regimens that will be more effective and of shorter duration to improve both the compliance and effectiveness of the treatment (6).

Alternative regimen recommended by the WHO is a single dose of rifampicin (600 mg), ofloxacin (400 mg), and minocycline (100 mg) (ROM) for PB leprosy patients with single lesion (2). Ofloxacin and minocycline are significantly more potent than dapsone and clofazimine against *M. leprae* and when combined with rifampicin provide a potent bactericidal activity that could kill 98% *M. leprae* in the first administration (7). Publication from the Philippines showed that 24 supervised monthly doses of ROM were proven to be safe, tolerable, provided similar clinical, bacteriologic, and histologic improvements to the MDT regimen. Furthermore, no skin pigmentation, increased rates of reactions, nor relapses after five years of follow-up were found (6).

Pathogenesis for nerve impairment in leprosy is still unclear, it is suspected due to *M. leprae* ability to modulate and induce cytokine production that cause Schwann cell apoptosis and ultimately cause nerve impairment in leprosy (8). In our case there was sensoric and motoric improvement in our patient. This improvement is due to minocycline effect that could repair acute nerve impairment. Minocycline is known to have antiapoptotic and immunomodulator effect, as well as the capacity to inhibit proteolysis, angiogenesis and collagen degradation which makes it the right choice for axonal degeneration management. In addition, Minocycline also has a higher bioavailability in the nerve tissue and skin due to its lipophilic nature (9, 10). There was a study that showed minocycline as an alternative option to prevent permanent disability in acute nerve impairment (<6 months) and in a patient who was unresponsive to corticosteroid. Around 80% of subjects showed complete or partial recovery in acute nerve impairment caused by leprosy (10).

This new alternative regimen is especially useful for patients who are concerned about clofazimine-induced skin pigmentation, compliance issues, sensitivity to an MDT component and it could potentially provide faster improvement. The downside of this regimen is that ROM treatment is expensive, thus preventing its mass administration and

MDT is free, i.e. provided by the government (6). One of the reasons one of our patients refused to have MDT regimen was pigmentation caused by clofazimine, whereas the patient with PB refused MDT regimen because he wanted to search for an alternative regimen that was faster, and simpler.

Unfortunately, a meta-analysis comparing monthly doses of ROM to MDT in MB leprosy patients did not provide sufficient data to conclude the efficacy of ROM therapy in MB patients. Thus, an additional study is required to evaluate effectiveness of this regimen in MB leprosy (3). Nonetheless, from our experience, the patients treated with ROM regimen 3 times weekly displayed satisfactory outcome due to the absence of skin pigmentation, similar effectiveness, and potentially shorter treatment durations. To that end we administer ROM given 3 times weekly to the patients who refuse MDT regimen recommended by the WHO and, as in the case above, it yields significant clinical improvement. Not only do the lesions disappear but this regimen could also improve the patient's sensory and motor problem subjectively.

Conclusion

ROM regimen given 3 times weekly for 6 weeks for PB leprosy and 12 weeks for MB leprosy showed significant clinical improvement in our leprosy patients. Thus, ROM regimen could be a more effective, safer, faster alternative treatment than MDT regimen recommended by the WHO for leprosy. However, there are still insufficient data to come to a valid conclusion on this regimen. Thus, long-term randomized controlled trials using ROM therapy in leprosy are needed.

Reference

1. World Health Organization, Regional Office for South-East Asia. Guidelines for the diagnosis, treatment and prevention of leprosy. New Delhi: World Health Organization, Regional Office for South-East Asia; 2018.
2. Worobec SM. Current approaches and future directions in the treatment of leprosy. Res Rep Trop Med. 2012;3:79-91.
3. Setia MS, Shinde SS, Jerajani HR, Boivin JF. Is there a role for rifampicin, ofloxacin and minocycline (ROM) therapy in the treatment of leprosy? Systematic review and meta-analysis. Trop Med Int Health. 2011;16(12):1541-51.

4. Gautam VP. Treatment of leprosy in India. J Postgrad Med. 2009;55(3):220-4.
5. Lockwood DN, Cunha Mda G. Developing new MDT regimens for MB patients; time to test ROM 12 month regimens globally. Lepr Rev. 2012;83(3):241-4.
6. Villahermosa LG, Fajardo TT Jr, Abalos RM, Cellona RV, Balagon MV, Dela Cruz EC, et al. Parallel assessment of 24 monthly doses of rifampin, ofloxacin, and minocycline versus two years of World Health Organization multi-drug therapy for multi-bacillary leprosy. Am J Trop Med Hyg. 2004;70(2):197-200.
7. Ji B, Sow S, Perani E, Lienhardt C, Diderot V, Grosset J. Bactericidal activity of a single-dose combination of ofloxacin plus minocycline, with or without rifampin, against *Mycobacterium leprae* in mice and in lepromatous patients. Antimicrob Agents Chemother. 1998;42(5):1115-20.
8. Oliveira RB, Sampaio EP, Aarestrup F, Teles RM, Silva TP, Oliveira AL, et al. Cytokines and *Mycobacterium leprae* induce apoptosis in human Schwann cells. J Neuropathol Exp Neurol. 2005;64(10):882-90.
9. Garrido-Mesa N, Zarzuelo A, Gálvez J. Minocycline: far beyond an antibiotic. Br J Pharmacol. 2013;169 (2):337-52.
10. Narang T, Arshdeep, Dogra S. Minocycline in leprosy patients with recent onset clinical nerve function impairment. Dermatol Ther. 2017;30(1):e12404.

Alternativni tretman lepre kombinacijom *Rifampicin Ofloxacin Minocycline* (ROM) – Prikaz dva slučaja

Sažetak

Uvod. Lepra je oboljenje koje uglavnom zahvata kožu i periferne nerve, a rezultat je neuropatija i združene dugoročne posledice, uključujući deformitete i invalidnost. Prema klasifikaciji SZO, postoje dve kategorije lepre; paucibacilarna (PB) i multibacilarna (MB). Standardni tretman za lepru primenjuje MDT režim Svetske zdravstvene organizacije, uprkos njegovim brojnim nedostacima poput pigmentacije izazvane klofaziminom, hemato-loškim nuspojavama izazvanih dasonom, loše komplijanse zbog dugog trajanja lečenja, rezistencije na lekove i pogoršanje. Zadovoljavajući rezultati su prijavljeni u mnogobrojnim studijama i prikazima slučajeva u kojima je korišćen ROM. Pa ipak, još nema dovoljno podataka da se odredi optimalna doza i dužina trajanja režima ROM kao alternativnog tretmana za lepru. Prethodno iskustvo iz naše institucije govori da ROM režim primenjen tri puta nedeljno daje zadovoljavajući ishod. **Prikaz slučajeva.** Prikazujemo dva slučaja lepre lečene ROM režimom u

našoj instituciji. Prvi je slučaj PB lepre kod muškarca starog 64 godine koji je došao sa jednim ljuspičastim plakom na desnoj poplitealnoj flosi. Ispitivanje senzibiliteta pokazalo je hipoesteziju bez uvećanja perifernog nerva. ROM režim je uveden tri puta nedeljno u trajanju od šest nedelja i kod pacijenta je došlo do značajnog kliničkog poboljšanja na kraju tretmana bez reakcije ili pogoršanja sve do posle šest meseci posle tretmana. Drugi slučaj je bio MB lepra kod muškarca starog 24 godine sa kandžastom šakom na trećoj i petoj falangi desne ruke i hipoestetskim eritematoznim plakom na čelu. Histopatološki pregled je potvrdio graničnu lepru. Pacijenti su primili terapiju tri puta nedeljno sa značajnim kliničkim poboljšanjem posle 12 nedelja. **Zaključak.** ROM režim primenjen tri puta nedeljno u trajanju od šest nedelja kod PB lepre i 12 nedelja kod MB lepre dao je značajno kliničko poboljšanje. Stoga, ROM režim bi mogao da bude efikasniji, bezbedniji i brži alternativni tretman za lepru.

Ključne reči: Bolesti kranijalnih nerava; Ušni herpes zoster; Neuritis; Znaci i simptomi; Dijagnoza; Antivirusni lekovi; Retke bolesti

Received 2.09.2019.

Accepted 12.09.2019.