Comparison of Effectiveness between Rifampicin Ofloxin-Minocycline Regimen and Multidrug Therapy-World Health Organization in Multibacillary Leprosy Patients

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Abstract

Background: Multidrug therapy (MDT) which is recommended by the World Health Organization (WHO) for multibacillary (MB) leprosy patients has some side effects; it is given in 12 doses over 12–18 months. Patients who refuse or are contraindicated in undertaking MDT-WHO can be given alternative rifampicin-ofloxacin-minocycline (ROM) regimen for 24 months, whose side effects are less but more expensive. This study was conducted to compare the effectiveness between ROM and MDT-WHO regimen in the first 12 months based on the derivation in morphological index (MI) of acid-fast bacilli (AFB) in MB leprosy patient.
Methods: This was an observational analytical study with retrospective cohort method. Data was collected from medical records of MB leprosy patients in the Medical Record Installation and Morbus Hansen Clinic, Dr. Hasan Sadikin General Hospital Bandung. The overall derivation in MI in 12 months was assessed according to the type of therapy undertaken by the patient. Data was analyzed by Mann-Whitney U Test.
Results: A total of 59 data were selected out of 800 data of new leprosy patients based on the inclusion and exclusion criteria. Among those, 20 patients were treated by ROM and 39 by MDT-WHO. Derivation of MI occurred among both groups, but ROM regimen had higher percentage (94.83%) compared with MDT-WHO regimen (79.57%) with p value=0.003 ($p<0.05$).
Conclusions: ROM regimen has better effectiveness than MDT-WHO regimen in the first 12 months in MB leprosy patients. **[AMJ.2016;3(4):661–5]**

Keywords: Multibacillary leprosy, multidrug therapy, rifampicin-ofloxacin-minocycline (ROM)

Introduction

Leprosy is an infectious disease which attacks peripheral nerves, skin, and other organs such as eyes, respiratory tract, and kidney.[1] Based on the World Health Organization (WHO) report, 232.857 new cases were found in 2012 , which can be considered high.[2] Leprosy control effort was done by WHO to resolve the problem by giving antileprosy medicines. In 1982, the WHO Study Group on Chemotherapy of Leprosy for Control Progammes recommended multidrug therapy (MDT) that was given based on type of leprosy.[3] For multibacillary (MB) patients, rifampicin 600 mg, clofazimine 300 mg, and dapsone 100 mg are given each month, continued by clofazimine 50 mg and dapsone 100 mg every day. Regimen is given in 12 doses for 12–18 months freely.[4] Rifampicin is a strong bactericidal drug, which can eliminate *Mycobacterium leprae* (*M. leprae*) quickly, while dapsone and clofazimine are bacteriostatic drugs.[3]

The MDT-WHO for MB type leprosy has several weaknesses, such as darkening of skin color (copper-like), hemolytic anemia, methemoglobinemia, hypersensitivity, and low patient compliance.[5] Thus, for leprosy patients who refuse or have contraindication in using MDT-WHO, in 1997, WHO recommended alternative regimen consisting of 600 mg rifampicin, 400 mg ofloxacin 400 mg, and 100 mg minocycline given each month for 24 months.[4] Those medicines have bactericidal effect on M. leprae and rifampicin has the best bactericidal effect.[15] Besides, ROM regimen has

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less side effect, such as nausea and vomiting, better patient compliance, but higher price compare to MDT-WHO regimen.[6]

Evaluation of leprosy treatment can be performed by evaluating skin the slit smear examination, especially the morphological index (MI) of acid–fast bacilli (AFB) that might give useful information about medication response.[7]

Furthermore, Villahermosa et al.[9] conducted a study comparing the effectiveness between ROM and MDT-WHO regimen for 24 months in MB type leprosy patients in the Philippines. Both regimens showed the same result on both groups in every aspects examined such as clinical, bacteriological, and histopathological examination.[9] Additionally, Lockwood et al.[4] suggested that a study comparing both regimens on MB type leprosy patients for 12 months to increase patient compliance, is needed.[4]

This study was conducted to compare the effectiveness between ROM and MDT-WHO regimen for the first 12 months based on the MI score in MB type leprosy patients.

Methods

This was an observational analytical study using the retrospective cohort method from MB type leprosy patients' medical records who received ROM or MDT-WHO regimen medication for 12 months (12 doses). This study was reviewed and approved by the Health Research Ethics Committee, Faculty of Medicine Universitas Padjadjaran Bandung.

Table 1 Characteristics of Patients Who Got ROM Regimen Therapy and MDT-WHO Regimen Therapy

Characteristics	ROM Regimen		MDT-WHO Regimen	
	(n=20)	%	(n=39)	%
Sex				
Male	17	85.0	32	82.1
Female	3	15.0	7	17.9
Age group (year)	34.2		34.8	
Education	4	20.0	12	30.8
Elementary	4	20.0	8	20.5
Junior High School	10	50.0	19	48.7
Senior High School	2	10.0	0	0.0
Bachelor				
Occupation				
Photographer	0	0.0	1	2.6
Teacher	0	0.0	1	2.6
Labor	0	0.0	1	2.6
Retiree	0	0.0	1	2.6
Fruit Merchant	0	0.0	1	2.6
Food Merchant	0	0.0	1	2.6
Satay Merchant	0	0.0	1	2.6
Street Vendor	0	0.0	1	2.6
Meatball Merchant	1	5.0	0	0.0
Farmer	1	5.0	0	0.0
Tombstone Maker	1	5.0	0	0.0
Factory Worker	1	5.0	2	5.1
Army	1	5.0	2	5.1
Employee	1	5.0	3	7.7
Entrepreneur	1	5.0	4	10.3
Unemployed	1	5.0	9	23.1
Housewife	2	10.0	5	12.8
Student	5	25.0	2	5.1
Professional Worker	5	25.0	4	10.3
Leprosy Type				
BB	4	20.0	1	2.6
BL	14	70.0	27	69.2
LL	2	10.0	11	28.2

Table 2 MI Mean Value in the Beginning and in the End for ROM Regimen Group and MDT-WHO Regimen Group

Variable	ROM Regimen (%)			MDT-WHO Regimen (%)		
	Mean		Stdev	Mean		Stdev
Initial MI	27.6	±	19.0	41.8	±	24.2
Final MI	1.4	±	5.4	8.5	±	12.3

Note: ROM = Rifampicin-Ofloxacin-Minocycline; MDT-WHO = Multidrug therapy WHO; MI = Morphological Index, Stdev = Standard Deviation

Data were taken from the Medical Record Installation and Morbus Hansen Clinic, Dr. Hasan Sadikin General Hospital Bandung. This study was conducted from March to November 2012. The period of data included in this study was from 1999 to 2013, including patients' identity, type of medication, and MI score.

All samples were included by total sampling method. Inclusion criteria in this study were new MB type leprosy patients who received ROM regimen therapy for minimal 12 months (12 doses) and MDT-WHO regimen for 12 months (12 doses), aged over 15 years , and had completed MI. Patients whose initial therapy were different from the last therapy (MDT-WHO regimen therapy changed to ROM regimen therapy or vice versa) were excluded from the study.

The final data was divided into two groups, ROM regimen group and MDT-WHO regimen group. The minimal data from each group was 20 samples based on the sample size formula for unpaired analytic-categorical study. All groups' AFB MI scores were determined before the medication started and after the medication was completed after twelfth month of medication.

After all the data needed was complete, an analysis was firstly started with data of normality test, continued with the bivariate analysis, namely Mann-Whitney U Test. Data analysis was performed using a statistical software while tables were made in Microsoft Excel.

Results

In this study, there were 800 new leprosy cases during the period of 1999 to 2013. There were 59 out of 800 data of new leprosy patients which met the inclusion and exclusion criteria consisting of 20 patients who were included in the ROM regimen group, while 39 patients were placed into the MDT-WHO regimen group. Furthermore, the disease affected male more than female in both groups, with not much mean age difference between those two groups. The majority of the patients' latest education for both groups was senior high school, with various occupations in each group. While, the borderline lepromatous was the leprosy type with the highest prevalence for both groups according to Ridley-Jopling classification (Table 1).

The initial and final MI mean score of both groups showed that each regimen had a gradual decrease of MI score. Based on those mean, the decrease of the MI percentage was counted. The decrease of MI score for ROM regimen and MDT-WHO regimen groups were 94.83% and 79.97% respectively (Table 2).

Moreover, normality test was performed on both groups using Shapiro Wilk test. P value of Shapiro Wilk test for both regimens was below 0.05, thus, the data was assumed to be abnormally distributed.

Then, Mann-Whitney U Test was performed to compare both groups. The comparison of the effectiveness between ROM regimen and MDT-WHO regimen's p value in the final month was 0.003 ($p<0.05$). This indicated that the effectiveness of ROM regimen was significantly better compared to MDT-WHO regimen for the first 12 months based on MI score decrease in MB type leprosy patients.

Discussion

Based on the patients' characteristics showed in Table 1, most patients who received MDT-WHO regimen therapy were unemployed. The drug price may become a differentiating factor in choosing the drug regimen for the leprosy patients despite the side effect and drug consumption frequency.[9] The ROM regimen has a higher price with less side effects (nausea and vomiting), with once in a month drug consumption, making it more simple for the patients compare to MDT-WHO regimen which needs to be consumed every day with more side effects (skin hyperpigmentation, hemolytic anemia, methemoglobinemia, hypersensitivity reaction), but given freely.[10] Based on those considerations, occupations

might be considered as an influencing factor in choosing leprosy medication regimen, therefore a further study needs to be conducted to prove this.

Therapeutic effectiveness comparison between ROM regimen and MDT-WHO regimen based on MI score decrease in 12 months for MB type leprosy patients was performed in this study. The result showed that MI score was decreased in both regimens, but it was more significant in ROM regimen (p value=0.003).

Both ROM and MDT-WHO regimens have rifampicin as a strong bactericide, therefore comparing other drugs in both regimens (ofloxacin and minocycline to dapsone and clofazimine) needs to be done.[11] A previous experimental study in neonate rats without thymus gland and infected with *M. leprae* showed that ofloxacin and minocycline were significantly more potent compared to dapsone and clofazimine in eliminating *M. leprae*.[12] Dapsone and clofazimin are bacteriostatic agents while minocycline and ofloxacin are strong bactericidal agents, thus, the latter two medicines can eliminate *M. leprae* quickly and significantly.[13]

Furthermore, a clinical trial study about pefloxacin and ofloxacin conducted by Fajardo et al.[15] in Cebu, the Philippines on *M. leprae* injected footpad mouse showed that *M. leprae* viability was decreased in the fourteenth to twenty-eighth day of study. In the fifty-sixth day, all patients who received ofloxacin did not have morphologically completed *M. leprae* on skin slit examination. This implied that fluoroquinolon medications, which includes pefloxacin or ofloxacin are strong bactericidal and act to eliminate *M. leprae* more quickly compared to dapsone dan clofazimin.[15] However, fluoroquinolon given in a single dose is not significant in eliminating *M. leprae* and it becomes more significant when combine to rifampicin. Moxifloxacin and pefloxacin have better bacterial eliminating ability compared to ofloxacin.[16] Even so, these days, ofloxacin is still more widely used compared to the other two medicines. This result can become a consideration for usage of moxifloxacin or pefloxacin in the future.[15]

A study conducted by Gelber and Grosset [16] also showed that minocycline can eliminate *M. leprae* more quickly compared to dapsone and clofazimin, slower than rifampicin, and similar with ofloxacin/pefloxacin.[16] Based on a clinical study in rats, showed that less *M. leprae* live in rats who received minocycline compared to rats who received dapsone dan clofazimin.[17]

Despite having a strong bactericidal property, ROM regimen also has lesser side effects compared to MDT-WHO regimen. Several studies stated that ROM regimen side effects are less common to MDT-WHO which contains dapsone and clofazimin.[18]

Limitations of this study were the loss of many medical records which lead to smaller sample size, incomplete MI records, and difference in patients' compliance to control their ilness regularly. It is recommended to conduct similar study with histopathological and serological examinations using prospective cohort design.

In conclusion, ROM regimen is more effective compared to MDT-WHO regimen for the first 12 months based on MI score on MB type leprosy patients. This study implies that ROM regimen may be considered to be used for 12 months in clinical practice.

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