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Research Article

Treatment of Leprosy Patients using Combination of Rifampicin-Clarithromycin for 3 Months in Tugurejo General Hospital Semarang

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Abstract

Background: Leprosy is a chronic disease which needs a life-long treatment. A long term treatment may cause drop-out patient because of the lack of patient's compliance. Therefore a safe and effective short-term treatment is necessary for the leprosy patients.

Objective: To determine the effectiveness of short-term treatment with combination regiment of rifampicin and clarithromycin for 3 months.

Method: This was a prospective cohort study with pre and post test design. At 337 leprosy patients previously untreated were given combination regiment of Rifampicin 600 mg monthly and Clarithromycin 250 mg twice daily for three months. Acid-fast bacilli smears, improvement rate, and adverse effects were assessed on the first, second, and third month.

Results: Acid-fast bacilli positivity rate showed a significant reduction ($p<0.05$) after 3 months of treatment and the improvement rate showed a significant increase ($p<0.05$). There were no significant adverse effects reported by the patients.

Conclusions: The combination regiment Rifampicin 600 mg monthly and Clarithromycin 250 mg twice daily for three months may be considered as an effective and safe short-term treatment for leprosy patients.

Keywords: Clarithromycin; Leprosy; Rifampicin

Introduction

Leprosy is a chronic disease caused by *Mycobacterium leprae*. It is primarily located on the skin and peripheral nerves, but may also be located on the mucosa of the mouth, eyes, upper respiratory tract, lymph nodes, testes, joints, muscles and bones [1,2]. The disease is one of amongst many public health problems in Indonesia, [3] which can cause permanent disability, discrimination and social stigma [4]. Therefore, it is necessary to have an integrated and comprehensive eradication program, including the finding of the patient as early as possible, appropriate treatment of leprosy and rehabilitation [3]. For the treatment of leprosy, the WHO in 1997 has recommended multi drugs therapy (MDT). In the implementation of MDT-WHO program there are some problems that arise e.g.: resistancy and drop out problem due to the long duration of treatment that affects patients' compliance in taking the drug, especially for the type of MB. Therefore, new drugs are required with different bactericidal mechanisms with drugs in current WHO-MDT regimen [5]. Several new drugs that have been examined and have bactericidal action are clarithromycin, ofloxacin, and minocycline [6]. These drugs are known to have high bactericidal effects against *M. lepra,* is easier to use and can shorten the duration of treatment [7].

One of the new anti-leprosy drug, clarithromycin, are known to be very active against the infection of *M. leprae* in humans and has the advantage of providing some clinical improvement, has high bactericidal activity, good tolerance and

rarely cause side effects [6,7]. This drug is rapidly absorbed in the gastrointestinal tract and converted into its active metabolite 14-hidroxyclarithromycin form of which inhibit the synthesis of bacterial protein by binding with the 50 S ribosomal subunit, thus preventing the elongation of the protein chain [8]. Leprosy patients type MB treated with clarithromycin 500 mg per day showed same clinical & bacteriological response to ofloxacin & minocycline [5]. Dose of 500 mg of clarithromycin per day for the lepromatous leprosy patients will kill 99% leprosy bacilli in 28 days and 99.9% in 56 days [9,10].

The purpose of this study was to determine the effectiveness of short-term treatment regimens of combination between rifampicin 600 mg per month and clarithromycin 2x250 mg per day for 3 months in new leprosy patients who had never been treated in Tugurejo General Hospital, Semarang.

Materials and Methods

Research subjects are consisted of leprosy patients who are treated at leprosy policlinic in Tugurejo Hospital, Semarang from the year 2004 until 2008. Diagnosis is based on clinical and bacteriological examination. The classification is based on the Ridley and Jopling. This study selected patients aged 15-85 years who had never received treatment and are willing to follow the study through to completion. Research carried out by using a prospective cohort of experimental methods with pre-and post-test study. Patients given a combination regimen of treatment with rifampicin 600 mg per month and clarithromycin 2x250 mg per day for 3 months in both PB and MB patients. This study conducted an assessment of patients' clinical and bacteriological cure. Observations were made every month for 3 months. Clinical cure is assessed based on the activity of lesion that is erythema, edema, diffuse infiltration, size or elevation nodules and plaques, and nerve involvement.

Results

During the study 337 patients of leprosy were found. Based on the description of subjects' analysis of respondents based on gender, the study found 240 men patients (71%) and 97 women patients (29%) (Table 1).

No.	Group	Frequency	Percentage
1	Men	240	71%
2	Women	97	29%
	Total	337	100%

Table 1: Grouping of subjects based on gender.

Based on the criteria of age, respondents between age 25 - 34 years have a high percentage of 28%, ages 15 - 24 years is 24%, ages 35 to 44 years is 13%, while age above 55 years had a low percentage (Table 2).

No.	Age Grouping	Frequency	Percentage
1	15-24 yrs	80	24%
2	25-34 yrs	96	28%
3	35-44 yrs	69	20%
4	45-54 yrs	43	13%
5	55-64 yrs	29	9%
6	65-74 yrs	12	4%
7	75-85 yrs	8	2%
	Total	337	100%

Table 2: Grouping of subjects based on age.

While the classification of leprosy according to Ridley and Jopling, respondents with the type BL have higher numbers of about 178 people, or by 53%, respondents to the type of BT leprosy of 145 people or 43%, respondents to the type of TT leprosy of 7 people or 2%, whereas respondents with type LL leprosy only 7 people or 2% (Table 3)

No.	Type MH	Frequency	Percentage
1	TT	7	2%
2	BT	145	43%
3	BL	178	53%
4	LL	7	2%
	Total	337	100%

Table 3: Respondents who suffer from leprosy by Ridley-Jopling classification.

Clinical assessment to assess the recovery rate is based on the active lesions of erythema, edema, diffuse infiltration, size or elevation nodules and plaques, and nerve involvement. This assessment is carried out in the first, second and third month. In the first month, the clinical improvements less than 50% are obtained in 21 people (6%), between 50-75% in 30 people (9%) and more than 75% in 286 people (85%) (see Table 4)

No	Recovery in 1st Month (in %)	Frequency	Percentage
1	<50	21	6%
2	50-75	30	9%
3	>75	286	85%
	Total	337	100%

Table 4: The level of clinical recovery in the first month of treatment.

In the second month, the clinical improvements less than 50% are obtained in 14 people (4%), between 50-75% in 30 people (9%) and more than 75% in 293 people (87%). (see Table 5)

No	Recovery in 2nd Month (in %)	Frequency	Percentage
1	< 50	14	4%

2	50-75	30	9%
3	>75	293	87%
	Total	337	100%

Table 5: The level of clinical recovery in the second month of treatment.

In the third month, the clinical improvements less than 50% are obtained in 6 people (2%), between 50-75% in 25 people (7%) and more than 75% in 306 people (91%) (see Table 6)

No	Recovery in 3rd Month (in %)	Frequency	Percentage
1	< 50	6	2%
2	50-75	25	7%
3	>75	306	91%
	Total	337	100%

Table 6: The level of clinical recovery in the third month of treatment.

In addition to clinical assessment was also carried out an assessment of the smear test to respondents to assess the effectiveness of combination drug therapy Rifampicin clarithromycin. Based on statistical calculations it can be concluded that administration of a combination drug therapy Rifampicin - clarithromycin proved to be effective on reducing smear laboratory test results provided in leprosy patients during 3 (three) months. Effectiveness is seen from the calculated t-test smear in the first month that shows the value of 786.33, the second month shows the value of 399.77 (down to 446.56 or 56, 80% from the first month), and the third month pointing to the value of 108.06 (down 231.71, or approximately 57.96% from the second month). Thus, it can be concluded that the therapy with drug combination of Rifampicin - clarithromycin is proved to be effective in the decrease or reduction of smear test results in leprosy patients from month I-III ($p < 0.05$). The level of recovery from the moon I, II and III tend to experience a significant increase ($p<0.05$). (Table 7). Side effects are not found in this study. Figures 1-4 showing before treatment and after three months therapy treatment.

No	Component	1st Month	2nd Month	3rd Month	Description
1	Smear Test	786.33	339.77	108.06	Tend to be negative
2	Cure Rates	134.84	149.00	153.71	Rise

Table 7: Statistical calculations of the smear test and cure rates.

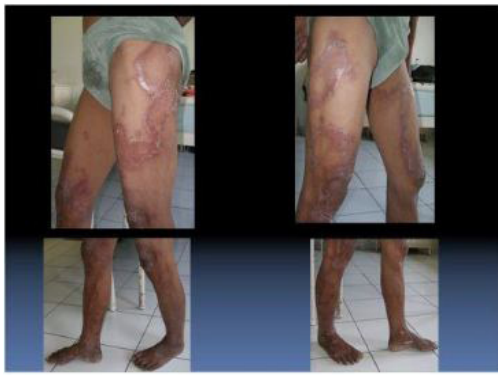

Figure 1: Before Treatment.

Figure 2: After 3 months of therapy.

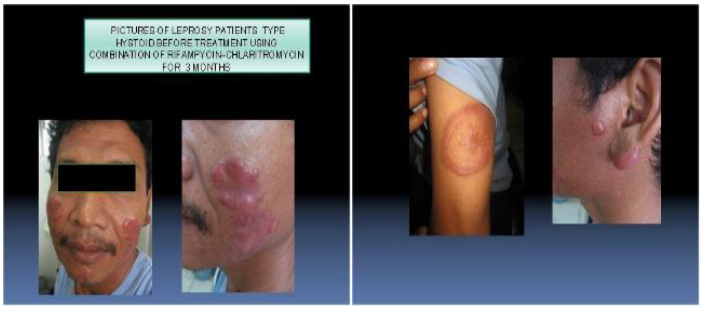

Figure 3: Leprosy patients type hystoid before treatment using combination of Rifamycin and clarithromycin for three months.

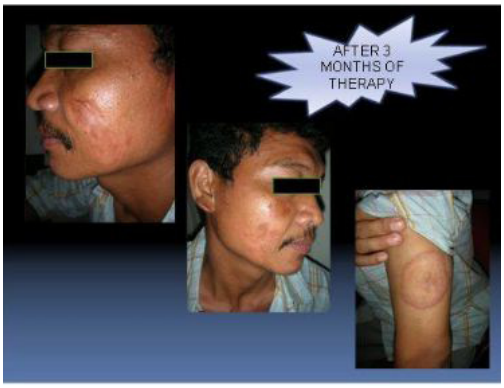

Figure 4: After 3 months of therapy.

Discussion

Since there are many difficulties in the implementation of MDT-WHO program, it is necessary to find a program that is simpler, shorter and easier for the patients. Therefore, it is important to look for new anti-leprosy drugs with higher bactericidal activity than standard regimens. Starting in mid-1980, a bactericidal activity from new fluoroquinolon (pefloxacin and ofloxacin), new macrolide namely clarithromycin and minocyclin has been observed. Compared to dapson and clofazimin, the new drugs are considered to have more bacterial activity. Only rifampicin has a higher effect than the new drugs in experiments on rats [11].

Rifampicin is a strong bactericidal drug. Rifampicin works in inhibiting the irreversible binding of enzyme RNA polymerase [2]. Single dose of 10-15 mg / kg BW can kill 99.9% germs within a few days. Provision of 600 mg or 1200 mg once a month is well tolerated [5]. The new drug is clarithromycin has a bactericidal effect equivalent to ofloxacin and minocycline. Chan GP and his colleagues in 1993 conducted a research by using clarithromycin therapy in 9 LL patients who had never any treatment. The dosage used is 2x1500 mg day-to-1 in the first week and then resumed in 1000 mg / day on days 8-21 (for 2 weeks) and on days 21-56 they use dose 500 mg / day. In this study the results obtained morphological index decreased in the first week after the initial dose, and decreased serum PGL-1 in the third week and significant clinical improvement at week 4, the drug is well tolerated and have only little side effects [12].

On the other hand, research using a combination regimen rifampicin-clarithromycin has not been made yet. A previous study by Wiraguna and Soebono in the year of 1990-1993 conducted by using a combination of rifampicin-ofloxacin compared with the WHO MDT regimen for 3 months, found that there were no significant differences between the two regimens wither in clinical assessment, bacterial index and serological ratings but 3 months is not enough to evaluate the efficiency of a treatment regimen in leprosy [13]. Based on the above, we do research by using a combination regimen rifampicin-clarithromycin for 3 months.

Tanasal in 2005 stated that short-term combination therapy rifampicin 600 mg per month and clarithromycin 2x250 mg per day for 3 months had succeeded to lower IgM titer significantly in subclinic leprosy patients [14]. Also, there is a report of type BL leprosy cases treated with the same regimens, improvement in clinical and in bacteriological index is found (Utama YD et al in 2007) [15]. Another report of leprosy histoid case treated with this combination regimen, clinical improvements and bacteriological results are obtained quite satisfactory. This combination therapy can be an alternative therapy in leprosy histoid especially because often there is resistance to dapsone (Pridady NS et al. in 2008) [16].

In this study the effectiveness of combination therapy rifampicin-clarithromycin in 337 leprosy patients is judged on clinical recovery and smear examination. At the level of clinical recovery, starting from the first until the third month there were increased levels of significant recovery. Comparison of smear examination between the first month and the third month showed significant decline.

Conclusion

Combination therapy with rifampicin-clarithromycin regimen in 337 leprosy patients in Tugurejo general hospital, Semarang for 3 months proved to be effective. This can be seen from the clinical cure that increased significantly from the first month until the third month and also from the decrease smear examination from first month to third month. This regimen can be considered to be sufficient in the treatment of leprosy patients.

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