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Original Article

Scenarios warranting modified treatment regimens in leprosy: A 5-year retrospective study from a tertiary care center

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ABSTRACT

Objectives: To study the scenarios warranting modified treatment regimens in leprosy.

Materials and Methods: A 5-year retrospective study was carried out in a tertiary care center by analyzing the data collected from national leprosy eradication program (NLEP) records.

Results: During the 5-year study period, 171 patients received treatment for leprosy from our center. Thirty-one patients (31/171, 18.1%) required substitution of standard multidrug therapy (MDT) with alternate drugs or required alternate treatment regimens. The patients who required modified treatment included 18 men (18/31, 58.1%) and 13 women (41.9%). Male/female ratio was 1.4:1. Indications for treatment modification were adverse drug reactions to standard MDT (ADR) (21/31, 67.7%) and lack of response to standard MDT (10/31, 32.3%). The most common scenario that warranted a modification of standard MDT was dapsone-induced hemolysis (12/31, 38.7%). Seven (7/31, 22.6%) and two (2/31, 6.5%) patients needed a change in treatment due to drug-induced hepatitis and drug-induced maculopapular rash, respectively.

Limitations: Retrospective study design, study conducted in single tertiary referral center and small sample size were the limitations.

Conclusion: Nearly one-fifth of patients with leprosy required modifications in standard MDT. The most common indication (in two-third of patients who needed a modified treatment) for modification of treatment regimen was adverse drug reactions.

Keywords: Multidrug therapy, Alternate regimen, Drug reaction, Dapsone, Hemolysis

INTRODUCTION

Multidrug therapy (MDT) introduced by the World Health Organization (WHO) has brought down the prevalence of leprosy to <1 in 10,000 in most parts of the world.[1] The standard first line drugs used in leprosy are dapsone, clofazimine, and rifampicin.[2] These drugs have been proved to be very safe and effective for leprosy and can also be given during pregnancy.[2] The second line drugs used in leprosy are ofloxacin, levofloxacin, moxifloxacin, minocycline, and clarithromycin.[2]

Occasionally, adverse drug reactions including organ specific toxicity such as hemolysis and hepatitis, are reported following standard MDT, warranting a change in regimen and

alternate drugs.[2] Some adverse drug reactions such as rifampicin shock, dapsone-induced hemolytic anemia, drug-induced hepatitis and dapsone syndrome are absolute contraindications for the offending drug.[2] At the same time, it should be kept in mind that there are a few alternate drugs for leprosy compared to other diseases like tuberculosis; hence, a careful and judicious approach should be undertaken before implementing a change in treatment.

In this retrospective study, we aimed to find the scenarios that necessitated a change in standard MDT in patients with leprosy attending a tertiary referral center.

MATERIALS AND METHODS

This is a 5-year (2018–2022) retrospective descriptive study done in the dermatology department of a tertiary care center. The data were collected from the National Leprosy Eradication Program (NLEP) records maintained in the department after masking personal identifiers. The study participants included all the leprosy cases (diagnosed by the World Health Organization cardinal criteria for leprosy), who attended the dermatology department during the study period and who required a modification in standard MDT.[2] Ethics and Research committees of the institution has waived the ethical approval for this study.

Using a pre-set proforma, we collected data on age, gender, clinical details such as type of leprosy, lepra reactions, and Grade 2 disability at diagnosis. Details of baseline investigations including complete hemogram, liver function test (LFT), renal function test (RFT), serology for human immunodeficiency virus (HIV) infection, and hepatitis B and C infections, and findings on chest radiography were noted.

As per institutional policy, all the patients were advised follow-up evaluation of complete hemogram, LFT, and RFT. They were repeated 1 week after starting treatment and if found normal, repeated every month thereafter. Patients who showed abnormal laboratory parameters were evaluated further to identify the cause. Hemolytic anemia was defined as a reduction of hemoglobin and hematocrit values to <42% in males and <36% in females from the baseline or by a combination of anemia, unconjugated hyperbilirubinemia, elevated reticulocyte count, and lactic dehydrogenase levels.[3] Patients who developed chest pain, palpitation, dyspnea, and cyanosis after starting dapsone were evaluated for methemoglobinemia by spectrophotometry. Hepatic abnormalities were defined as bilirubin more than 1.2 mg/100 mL, or an increase in the serum levels of aminotransferases, gamma-glutamyl transpeptidase, or alkaline phosphatase to more than twice the upper limit of normal. The indication for modifying the standard regimen was noted along with the drugs received by the patient.

Patients with paucibacillary (PB) leprosy received monthly rifampicin (600 mg) and daily dapsone (100 mg) for 6 months, while multibacillary (MB) patients received monthly rifampicin, daily dapsone, and clofazimine (50 mg daily and 300 mg once a month) for 1 year.[2] Lack of response to standard MDT was defined as persistence of the initial lesions, appearance of new lesions in the absence of lepra reactions, patient not showing 2 log fall in bacterial index (BI) or showing a morphological index (MI) >0 after completion of standard MDT or a post-treatment biopsy showing live acid-fast bacilli.[2] The cause for lack of response to treatment was kept as due to persisters/drug resistance, if patient had taken regular and adequate treatment. A definite diagnosis of drug resistance to standard MDT was made only when the former was proven by appropriate laboratory work up.[2]

Protocol for change in regimen

Whenever hemolytic anemia was diagnosed, dapsone was substituted with clofazimine in PB treatment, whereas patients receiving MB regimen received ofloxacin instead of dapsone.[2] When hepatitis was diagnosed, both dapsone and rifampicin were withdrawn. LFT was repeated after 2 weeks and if found normal, the next monthly dose of rifampicin was given as per schedule (all the while avoiding dapsone). A repeat LFT was done 2 weeks after the monthly dose of rifampicin. If LFT showed normal values, the patient was considered to have dapsone-induced hepatitis. We substituted dapsone with clofazimine in PB regimen and substituted dapsone with ofloxacin in MB regimen.[2] If repeat LFT (after 2 weeks of monthly rifampicin without dapsone) showed abnormal values, the patient was treated with the WHO alternate regimen: clofazimine 50 mg, ofloxacin 400 mg, and minocycline 100 mg daily once a day per orally for 6 months followed by clofazimine and ofloxacin for the next 18 months and the patient was considered to have dapsone/rifampicin- induced hepatitis.[2]

The data were entered in Microsoft excel sheets and analyzed. The qualitative variables were expressed in terms of frequency and percentage, while the quantitative variables were expressed as mean and standard deviation.

RESULTS

During the study period, 171 leprosy patients received treatment from our center. Thirty-one patients (31/171, 18.1%) required a change in treatment regimen. The mean age of the study participants was 41.3 years (standard deviation 16.5 years). The most common age group was 21–30 years (8/31, 25.8%). The youngest and the oldest were aged 16 years and 72 years, respectively. There were 18 males (58.1%) and 13 females (41.9%) with a male to female ratio of 1.4:1.

The salient clinical features observed are given in Table 1. Borderline tuberculoid (BT) leprosy was the most common

type of leprosy (14/31, 45.2%). None of the patients manifested mid-borderline leprosy or indeterminate leprosy.

Twenty-nine patients (29/31, 93.5%) were initially started on standard MB-MDT, while 2 cases (2/31, 6.5%) received PB-MDT. Five patients (5/31, 16.1%) received systemic steroids for lepra reactions.

Adverse drug reactions such as dapsone-induced hemolysis, drug-induced hepatitis, and maculopapular drug rash were the reasons for the change in regimen in 21 cases (67.7%). Lack of response to standard MDT necessitated a change in regimen in 10 cases (10/31, 32.3%).

The factors which warranted a change of regimen are given in Table 2. The most common indication for change in MDT was dapsone-induced hemolytic anemia, accounting for 12 cases (12/31, 38.7%, Table 2). Drug-induced hepatitis was noted in seven patients (7/31, 22.6%). In four out of the seven patients (4/7, 57.1%), dapsone was identified as the drug producing hepatitis, whereas in three others (3/7, 42.9%), we made a diagnosis of dapsone/rifampicin-induced hepatitis. Two patients (2/31, 6.5%) needed a change in treatment due to maculopapular drug reaction suspected to be due to dapsone or rifampicin (exact offender remained unclear as drug re-challenge was not performed).

Most of the patients who manifested dapsone-induced hemolytic anemia had BT leprosy (6/12, 50%).

One LL (lepromatous leprosy) patient (1/31, 3.2%) had mutation imparting drug resistance to rifampicin (mutation in rpoB gene). The treatment regimens received by the study participants are shown in Table 3. The most common modified treatment offered was the 2-year clofazimine-ofloxacin-minocycline regimen (13/31, 41.9%).

Table 1: Clinical manifestations in leprosy patients who required modifications to standard mutltidrug therapy.

Clinical manifestations	Number of patients (percentage of total) *n*=31 (100%)
Type of leprosy	
Indeterminate leprosy	0 (0%)
Pure neuritic leprosy	1 (3.2%)
Tuberculoid leprosy	1 (3.2%)
Borderline tuberculoid leprosy	14 (45.2%)
Mid-borderline leprosy	0 (0%)
Borderline lepromatous leprosy	4 (12.9%)
*Lepromatous leprosy	11 (35.5%)
Type 1 lepra reaction	1 (3.2%)
Type 2 lepra reaction	2 (6.5%)
Grade 2 disability at diagnosis	2 (6.5%)

*One patient had histoid leprosy

DISCUSSION

This 5-year retrospective study found that 18.2% of patients, who received MDT for leprosy needed either a modified regimen or an alternate regimen and the proportion fell between the same reported in the previous studies (3.1–45%).[4-6] The present study also gathered information on lack of response to treatment, which necessitated a change in regimen, while most of the previous works were limited to adverse drug reactions to MDT.[4-6] Comorbidities such as hepatic or renal disease or glucose-6 phosphate dehydrogenase (G6PD) deficiency may also require a change in anti-leprosy treatment regimen. However, none of the patients in this study had baseline hepatic or renal function abnormalities. We do not have data on G6PD deficiency in study participants as the institution does not have the facility to assess the same.

BT leprosy was the most common type of leprosy in patients who required a change in standard MDT, which was comparable to previous studies.[3,7] We noted hemolysis and hepatitis as the major causes that warranted a change in treatment regimen. The proportion of study participants who had dapsone-induced hemolysis (38.7%) was comparable to the existing studies (12.3–56.5%).[3,7] Dapsone-induced hemolysis, being the most common indication for modification of standard MDT as noted by us, was comparable to literature.[8] Drug-induced hepatitis necessitated a change in MDT in 22.6% patients which was lower than the 30.1–35.3% reported by others.[6] Both dapsone and rifampicin are hepatotoxic drugs. Often, it is difficult to pinpoint the exact offender, though in most cases, it has been found to be dapsone.[9] In the setting of detection of altered LFT after MDT, the standard protocol is to stop both rifampicin and dapsone. If repeat LFT after 2 weeks shows normal value, rifampicin is re-introduced and LFT is monitored weekly or fortnightly. If the LFT remains normal, rifampicin is continued without dapsone. This procedure is very important as rifampicin is the most effective drug against *Mycobacterium leprae* and needs to be given only once a month, unlike dapsone, which is required daily.[2] The limited options in management of leprosy make it important to avoid false assumptions of drug intolerance. There were two cases of maculopapular drug reaction and the suspected drugs were dapsone or rifampicin. In cases of suspected drug reaction to standard MB-MDT, it is always advisable to substitute dapsone and rifampicin (when exact offender not identified by a drug re-challenge test); however, clofazimine can be continued as it is not known to cause severe adverse drug reactions.[10]

There were 10 cases of non-responders to standard MB-MDT in this study. This lack of response could be due to drug defaulting by patients or due to persistent bacilli, or due to drug resistance. In the above mentioned cases, there

Table 2: Indications warranting alternate regimen/ modifications to standard MDT regimen in leprosy patients.

Type of leprosy (Number of patients in each type, percentage)	Dapsone-induced hemolysis *n*=12 (%)	Drug-induced hepatitis *n*=7 (%)	Maculopapular drug reaction *n*=2 (%)	Non-responders to standard multidrug MDT (? cause) *n*=9 (%)	Proven case of drug resistance to rifampicin *n*=1 (%)
Pure neuritic leprosy (1, 100%)	1 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Tubeculoid leprosy (1, 100%)	0 (0%)	1 (100%)	0 (0%)	0 (0%)	0 (0%)
Borderline tuberculoid leprosy (14, 100%)	6 (42.9%)	5 (35.7%)	1 (7.1%)	2 (14.3%)	0 (0%)
Borderline lepromatous leprosy (4,100%)	1 (25%)	1 (25%)	1 (25%)	1 (25%)	0 (0%)
*Lepromatous leprosy (11, 100%)	4 (36.4%)	0 (0%)	0 (0%)	6 (54.5%)	1 (9.1%)

*One patient had histoid leprosy and the patient manifested hemolysis. MDT: Multidrug therapy

Table 3: Treatment given to leprosy patients who needed alternate regimen/ modifications to standard MDT regimen.

Type of leprosy (Number of patients in each type, percentage)	Rifampicin+ clofazimine	Rifampicin+ clofazimine+ ofloxacin	Rifampicin+ dapsone+ ofloxacin	*WHO alternate regimen
Pure neuritic leprosy (1, 100%)	1 (100%)	0 (0%)	0 (0%)	0 (0%)
Tuberculoid leprosy (1, 100%)	1 (100%)	0 (0%)	0 (0%)	0 (0%)
Borderline tuberculoid leprosy (14, 100%)	0 (0%)	7 (50%)	1 (7.1%)	6 (42.9%)
Borderline lepromatous leprosy (4, 100%)	0 (0%)	2 (50%)	0 (0%)	2 (50%)
*Lepromatous leprosy (11, 100%)	0 (0%)	5 (45.5%)	1 (9.1%)	5 (45.5%)

WHO: World Health Organization. WHO alternate regimen: clofazimine 50 mg, ofloxacin 400 mg and minocycline 100 mg daily for 6 months followed by clofazimine and ofloxacin for 18 months. *One patient had histoid leprosy and required rifampicin, ofloxacin and clofazimine. MDT: Multidrug therapy

were no recorded data of defaulters in the NLEP cards, but it is possible that some of these patients might have collected their blister packs; but failed to take the drugs regularly. Drug resistance could not be evaluated in all patients due to financial constraints and lack of facilities at our center (the evaluation for drug resistance in the single case was carried out at the Schieffelin Institute, Karigiri). However, the prompt response to treatment with the WHO alternate regimen or a combination of rifampicin-dapsone-ofloxacin (in patients who could not afford the daily minocycline recommended in the alternate regimen, Table 3) shown by all the non-responders indicates that at least a few more of them could be cases of drug resistance. The patient who showed rpoB gene mutation responded well to the alternate regimen.

Limitations

Retrospective study design carried out in single tertiary care center and small sample size were the limitations of this study. We could not evaluate for drug resistance in all those who showed inadequate response to standard MDT.

CONCLUSION

Intolerance to MDT or lack of response to treatment necessitated changes in standard MDT in approximately 20% of patients with leprosy during a period of 5 years. Dapsone-induced hemolysis was the most common indication for change in standard regimen.

Ethical approval

The Institutional Review Board has waived the ethical approval for this study.

Declaration of patient consent

Patient's consent not required as patients identity is not disclosed or compromised.

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Nil.

Conflicts of interest

Dr. Pradeep S. Nair is on the editorial board of the Journal.

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