Clinical and Histopathological Response to Multidrug Therapy in Paucibacillary Leprosy at the end of 6 Months: A Prospective Observational Study from Eastern India

Indrashis Podder, Abanti Saha, Debabrata Bandyopadhyay

Abstract

Background: At present, the WHO recommends fixed duration multidrug therapy (FD-MDT) for the treatment of leprosy, in which treatment is provided for a fixed duration regardless of clearance of skin lesions or bacterial status of the patient. There is divided opinion regarding the efficacy of FD-MDT; especially for paucibacillary Hansen’s disease, in which treatment is provided for 6 months. In addition, there is a paucity of literature on clinical and histopathological features of treated leprosy. Objectives: The objectives of this study were to prospectively observe the effects of MDT on clinical and histopathological features in paucibacillary leprosy and to assess the efficacy, safety and tolerability of MDT-paucibacillary (PB) regimen. Materials and Methods: A total of 52 new cases of PB leprosy diagnosed by clinicopathological correlation and slit skin smear were administered standard WHO PB-MDT for 6 months. Patients were reviewed at 3rd month and 6th month of therapy and 3 months posttherapy for their clinical and histopathological assessment. Results: Among 52 new cases of PB-leprosy 43 patients (mean age 31.74 ± 12.2 years, m:f 1.53:1) completed the study as per protocol. Fourteen percent patients recovered completely, 76.7% patients had a residual patch at the end. Number of lesions reduced significantly 2nd follow-up onwards while the lesional size showed significant decrease 1st follow-up onward. Nerve palpability also reduced significantly at treatment completion. Histological improvement was appreciable; lymphocytic infiltration reduced significantly 2nd follow-up onward and presence of granuloma 1st FU onward. Only four patients complained of occasional, uneventful epigastric pain during the study. Conclusion: Although the frequency of persistence of lesions after completion of therapy was high, histological evidence of activity was present in a minority (7%). Thus, the standard WHO MDT-PB regimen was found to be effective, safe and well-tolerated.

Key Words: Histopathological changes, paucibacillary, treated leprosy

Introduction

The World Health Organization (WHO) recommends a multidrug therapy (MDT) consisting of rifampicin and dapsone for a fixed duration of 6 months in paucibacillary (PB) leprosy patients regardless of the clearance of skin lesions or presence or absence of acid-fast bacilli in the skin. A considerable number of patients continues to harbour residual skin lesions even after the completion of the WHO MDT for 6 months, which serve as a source of great anxiety and concern to the patient and family. Several patients also develop new lesions after completion of treatment which may be regarded as relapse or late reactions.

Few studies exist at present to assess the efficacy, safety and tolerability of MDT PB regimen. Even fewer studies exist to address the histomorphological changes observed in the skin lesions in response to treatment. Histomorphological changes at treatment completion which indicate “active” disease include findings such as persistence of granulomas or selective perineural,
and periangnexal lymphohistiocytic infiltration in the absence of granulomas. On the other hand, some histological findings in patients who have completed the recommended MDT-PB regimen such as epidermal flattening with basal layer melanisation in a clinically hypopigmented patch, reduced or absence of dermal infiltration, upper dermal oedema, and fibromyxoid changes of dermal stroma indicate “inactive” disease.[1] These histological findings along with clinical correlation in conjunction with a history of treatment (MDT-PB) completion would help us to assess the status of treatment and that of the disease (active or inactive) in case of patients who present with persistent or new lesions after treatment completion. Some authorities have proposed a quantitative parameter called “granuloma fraction” to assess the status of the disease. To address these issues, we have studied in a group of PB leprosy patients from eastern India, the evolution of clinicopathological changes in the skin lesions during and at the end of the recommended course of treatment. The safety and tolerability of MDT-PB regimen have also been assessed during the study.

**Materials and Methods**

We recruited 52 consecutive newly diagnosed PB leprosy patients at a tertiary care centre in eastern India over a period of 1 year (2014-2015).

**Inclusion/exclusion criteria of patients for the study**

Newly diagnosed treatment-naive cases of PB leprosy patients were enrolled for the study. These included patients with 1–5 hypopigmented or erythematous skin lesions, with definite sensory impairment or anaesthesia, a maximum of one thickened/tender nerve, with or without histopathological findings suggestive of TT or borderline tuberculoid (BT) leprosy (perineural infiltration, granuloma, etc.) and a negative slit skin smear (SSS). Institutional Ethics Committee approval was obtained and all patients were required to sign an informed consent form. Children below 5 years, adults above 70 years, those with systemic comorbidities (e.g., hepatic impairment and renal impairment) and pregnant or lactating women were excluded from the study.

**Baseline evaluation**

All patients were subjected to thorough cutaneous and systemic clinical evaluation followed by SSS from earlobe and edge of the skin lesions, a punch biopsy specimen from the lesion, and routine haematology and biochemistry panel.

**Treatment**

All the recruited patients were administered the standard WHO-MDT PB regimen (for adults or children) for 6 months. A single dose of rifampicin and dapsone was given under supervision once a month while the patients were instructed to take dapsone daily on their own.

**Follow-up and assessment**

**Clinical assessment and scoring**

Patients were assessed at baseline and at 3rd month (1st FU), 6th month of therapy (2nd FU), and 3rd month posttherapy (3rd FU) for their clinical and histopathological assessment. Six clinical parameters were evaluated (Table 1), and scoring was done[5] to compare the results pre- and post-treatment. Cure of the disease was defined as complete resolution of the lesion or patch becoming flattened, hypopigmented with decrease in size of lesion, and/or regaining of sensation.[6] Slit skin smear was performed at treatment completion. Any adverse drug reaction (ADR) due to MDT was also noted during the visits. Routine haemogram and serum biochemistry panel were also tested on each visit.

**Clinical grading of outcome**

The clinical grading of each patient was done based on the percentile improvement of baseline clinical score; ≥90%, 60%–90%, 30%–60%, and <30% improvement indicated resolution, good, moderate, and poor/no improvement, respectively.

**Histopathological assessment**

It was made on the basis of granuloma fraction (GF) which denoted the fraction of the entire dermis occupied by the granulomatous infiltrate.[4] GF >0.1 indicates histological activity, while histological resolution is denoted by GF <0.1. The absence of granuloma and/or <5% lymphocytic infiltrate indicated “inactivity”.

| Clinical parameter          | 0                  | 1                  | 2                  | 3                  |
|----------------------------|--------------------|--------------------|--------------------|--------------------|
| Hypopigmentation            | None               | Mild               | Moderate           | Marked             |
| Erythema                    | None               | Mild               | Moderate           | Marked             |
| Infiltration                | None               | Mild               | Moderate           | Marked             |
| Appearance                  | Not visible        | Doubtful           | Faintly visible    | Clearly visible    |
| Hypo/anaesthesia            | No loss/marked improvement | Doubtful/mild improvement | Definite loss/no improvement | Complete loss/worsening |
| Size of the lesion          | Marked reduction   | Mild reduction     | Baseline           | Increase in size   |

Table 1: Clinical scoring system
Statistical analysis
Demographic, clinical, and histopathological characteristics of the patients were evaluated, statistically analysed and compared before and after treatment. Statistical tests of significance were applied using Medical Software version 14 (USA). All the relevant information have been preserved for future reference.

Results and Analysis
A total of 52 new cases of PB Hansen’s disease were recruited for our study. Among them, 43 patients completed the study as per protocol and were included for further analysis.

Clinicodemographic profile of the patients
Males outnumbered females (m:f. 1.53:1), with a mean age of 31.74 ± 12.2 years. The proportion of childhood leprosy (<15 years of age) was 4.65% (2; n = 43). About 69.8% hailed from a rural background and 72.1% had income below the poverty line (BPL). About 32.56% of patients (14; n = 43) suffered for 1–2 years before seeking treatment.

Number and distribution of skin lesions
At start of therapy, 34 (79%) had single lesion, 5 (11.6%) had two lesions, and 4 (9.3%) had three lesions. Half of the patients (22; 51%) had lesions on the upper extremity, while 12 (27.9%) had lesions on lower extremity and 9 (20.9%) presented with facial lesions.

Morphology and evolution of lesions
While many patients (18; 41.09%) presented with patches with elevated borders before treatment, the patch was the predominant morphology post-treatment in 40 (93%) cases (n = 43).

Size of the lesions
There was significant reduction in the size of lesions 1st follow-up onward (Friedmann’s ANOVA, P < 0.001 with post hoc Dunn’s test P < 0.05).

Nerve involvement
Nerve involvement was noted in 35 patients (81.39% n = 43). Among them, 20 patients (57.14% n = 35) had ulnar nerve thickening. The common peroneal nerve was thickened in 7 cases (20%) (n = 35) while 18.6% of patients had thickening of some other nerve (supraorbital, facial, etc.) Nerve palpability reduced significantly with time (P < 0.0001, McNemar’s test).

Type 1 reaction (T1R)
Only six patients showed clinical and/or histopathological evidence of Type 1 reaction at baseline while two and one patient(s) showed evidence of reaction in the subsequent follow-ups [Figure 1]. Facial and neck lesions showed greater propensity to undergo Type 1 reaction which was found to be statistically significant (Yate’s Chi-square test; P = 0.014).

Slit-skin-smear examination
SSS and modified Ziehl-Neelsen staining was done for all cases at baseline and at end of therapy. All cases were SSS negative on both occasions, thus corroborating the diagnosis of PB Hansen’s disease.

Proportion of persistent lesions
Out of the 56 total lesions (baseline) studied in 43 patients, only 15 (26.79%) resolved completely at the end of study (3rd FU; 3 months after end of MDT) [Figure 2]. Fifty lesions persisted after 2nd FU (end of therapy). Forty one (73.21%) lesions persisted in 37 (86.05%) of the 43 patients at end of study, even after the prescribed course of WHO-MDT (PB) for 6 months.

Clinicopathological correlation
At the baseline, clinicopathological correlation was assessed. It was maximum (94.6%) for BT Hansen’s disease and least for TT Hansen (50%) [Table 2].

Analysis of histopathological changes
Epidermal thickness
Thirty-eight (88.4%) patients showed normal epidermal thickness; 5 (11.63%) showed atrophic epidermis in the baseline (pretreatment) biopsies. In the 1st FU

| Clinical diagnosis | Number of patients | Histopathological diagnosis | Correlation percentage |
|--------------------|--------------------|-----------------------------|------------------------|
| TT | 2 | 1 | 1 | 0 | 50 |
| BT | 37 | 2 | 35 | 0 | 94.6 |
| ID | 4 | 0 | 1 | 3 | 75 |
| Total | 43 | | | | |
biopsy (3 months after treatment), only 2 patients (4.7%) persisted with atrophic epidermis while the rest 41 (95.3%) showed normal epidermis. In the post-treatment biopsy (2nd FU), all patients showed normal epidermis.

**Nature of cellular infiltrate in the dermis**

The degree or extent of lymphohistiocytic infiltrate in the dermis was recorded and classified under the following heads, namely, normal (no infiltration), mild, moderate, diffuse, and focal infiltrations. Significant reduction of lymphocytic infiltration was noted 2nd FU onward ($P < 0.05$, Chi-square). The findings have been tabulated in table 3.

**Granuloma**

Granuloma is traditionally considered an important component of the histopathological picture of PB-Leprosy. However, in our study, only 34.9% of patients showed a granuloma in baseline histology. With treatment 14% and 6.9% showed granulomas at 1st and 2nd follow-ups, respectively [Table 4]. There was a significant reduction in the presence of granuloma 1st FU onward ($P < 0.05$, McNemar test) [Figures 3 and 4]. The presence of granuloma denotes active lesion; thus, three (6.9%) patients remained histologically active at completion of therapy.

**Assessment of the safety of multidrug therapy-paucibacillary therapy**

Laboratory parameters (Hb, total leukocyte count, platelet count, and SGPT) were within the normal ranges in all patients at all points of the study. Mild reduction of haemoglobin value was noted in six patients at end of therapy and four patients complained of occasional, uneventful epigastric pain toward the end, thus making this therapy safe and tolerable for the patients.

**Discussion**

We have performed an observational longitudinal study involving 43 patients. All the patients were analysed on their clinical response with special reference to histopathological changes observed before, during and after PB-MDT. The mean age of our study population was $31.74 \pm 12.2$ years with most cases ($46.51\%$) between 15 and 29 years. In a study conducted by Kumar *et al.*,[6] most patients ($21.6\%$) belonged to age group 35–44 years. Age distribution found in this study was similar to that reported in literature.[7] In almost all the studies, males have been affected more than females.[6] Thangaraj reported a male-to-female ratio of 2:1.[7] The current study also corroborated this data with a male:female ratio of 1.5:1.

In the present study, most patients ($69.8\%$) hailed from a rural background and belonged to the BPL category ($72.1\%$). The higher prevalence in this population may be attributed to low income, illiteracy, lack of awareness, poor treatment facilities, and transport difficulties. A similar finding was elicited by Kaur and Singh[8] and Chatterjee *et al.*[9]

Almost 79% of our patients presented with a single lesion at baseline. A similar finding was reported by Balagon *et al.*[10] However, 2–3 lesions were most commonly found in the study conducted by Kumar *et al.*[6] Number of lesions reduced significantly with treatment 2nd FU onward (Friedman’s ANOVA, $P < 0.001$ with post hoc Dunn’s test $P < 0.05$). The most common type of lesion seen in the present study was patch. A similar finding was elicited in most other studies.[11]
Majority of our patients (81.39%) presented with a palpable nerve at the initiation of therapy (ulnar > CPN); this figure is slightly higher than that reported by Kumar et al[6] which reported 66.4%. Nerve palpability reduced significantly with treatment ($P < 0.0001$, McNemar’s test).

A relatively high proportion (14%) of the lesions were in T1R at the time of diagnosis in this study as compared to published reports which indicate average frequency from 2.6% to 6.4%.^[10,12] This difference may be attributed to selection of only untreated PB cases. However, the proportion of T1R reduced with treatment, with only 2.3% patients showing features of T1R at end of treatment. This proportion is pretty high when compared to standard data (0.7%).^[6] An interesting statistically significant phenomenon noted in this study is the propensity of facial and neck lesions to undergo Type 1 reaction. This may indicate role of sunlight (UV rays) in precipitating acute reactional episodes. Large facial lesions have been described as a risk factor for development of Type 1 reaction in one study.[13]

In this study, BT leprosy was the most common clinical and histopathological type of PB leprosy. This is similar to findings of other authors.[11,14,15] In most of the cases, clinicopathological correlation was obtained.

Forty one of 56 (73.21%) lesions persisted in 37 (86.05%) of the 43 patients at end of study, even after the prescribed course of WHO-MDT (PB) for 6 months. The number of persistent lesions is expected to decrease further in the future as many studies quote self-improvement in lesions after completion of therapy. However, a longer duration of follow-up is needed.

There are many reports documenting persisting clinical activity in significant proportion of PB patients after 6 months of MDT ranging from 21.4% to 56%.[16-18] They have concluded that 6 months MDT is not adequate for all patients. However, a review of all reports concluded that PB-MDT for 6 months is adequate for most PB cases as delayed resolution is observed in many cases.[19]

In our study also, most of the persistent lesions were inactive on histopathological examination. Only three patients (6.98%) presented with active histological lesions at the end of treatment. Although inactive, these hypopigmented lesions are a source of anxiety to the patients. Hence, in such cases, patients should be counseled adequately rather than focusing on re-treatment.

In our study, granuloma was present in about 34.9% and 4.65% cases before and after treatment, respectively; which indicates active disease. Most cases (85%) showed normal epidermis, consistent with standard literature. Lymphocytic infiltration in the dermis reduced significantly 2nd FU onward ($P < 0.05$, Chi-square test).

In present study, histopathological resolution was found to be slower than clinical resolution in most cases. So even if a lesion has clinically subsided, it may or may not have resolved histologically at that point of time. Thus, mere presence of histological activity is not a criteria to restart MDT-PB; clinico-histological correlation must be done in such cases thus avoiding overuse of MDT-PB regimen.

This study depicted MDT-PB regimen to be safe and tolerable. Only four patients complained of occasional, uneventful epigastric pain toward the end, which was relieved without any specific intervention. There was no significant alteration of laboratory parameters as a result of MDT-PB. This finding is consistent with that of other studies.[6,20]

**Limitation**

A longer follow-up involving a larger sample size is needed to assess whether there is any relapse in these patients to have a better idea about the efficacy of MDT-PB.
of MDT-PB after 6 months and also the safety and tolerability of the same.

Declaration of patient consent
The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

What is new?
Fixed duration MDT is adequate if provided for 6 months in case of paucibacillary leprosy. Mere presence of histological activity is not a criteria to restart MDT-PB; clinico-histological correlation must be done to avoid overuse of MDT-PB regimen.

References
1. World Health Organisation. Global leprosy: An update on 2012 situation. Wkly Epidemiol Rec 2013;88:365-80.
2. Persistence of Skin Lesions after Completion of Uniform MDT in Leprosy: National Institute of Epidemiology. Available from: http://www.icmr.nic.in/annual/2004-05/nie/leprosy.pdf. [Last accessed on 2016 Jul 30].
3. Joshi R. Clues to histopathological diagnosis of treated leprosy. Indian J Dermatol 2011;56:505-9.
4. Cree IA, McDougall AC, Coghill G, Beck JS. Quantitation of the granuloma fraction in leprosy skin biopsies by planimetry. Int J Lepr Other Mycobact Dis 1985;53:582-6.
5. 2-3 Lesion Multicentre Trial Group. A comparative trial of single dose chemotherapy in paucibacillary leprosy patients with two to three skin lesions. Indian J Lepr 2001;73:131-43.
6. Kumar A, Girdhar A, Girdhar BK. A randomized controlled trial to compare cure and relapse rate of paucibacillary multidrug therapy with monthly rifampicin, ofloxacin, and minocycline among paucibacillary leprosy patients in Agra district, India. Indian J Dermatol Venereol Leprol 2015;81:356-62.
7. Thorat DM, Sharma P. Epidemiology. In: Kar HK, Kumar B, editors. IAL Textbook of Leprosy. New Delhi: Jaypee; 2010. p. 24-31.
8. Kaur P, Singh G. Deformities in leprosy patients attending urban leprosy clinic at Varanasi. Indian J Lepr 1985;57:178-82.
9. Chatterjee T, Halder A, Mishra R, Saha B. Study of certain social correlates in leprosy case. Indian J Community Med 2001;26:189.
10. Balagon MF, Cellona RV, Abalos RM, Gelber RH, Sauderson PR. The efficacy of a four-week, ofloxacin-containing regimen compared with standard WHO-MDT in PB leprosy. Lepr Rev 2010;81:27-33.
11. Pandya AN, Tailor HJ. Clinico-histopathological correlation of leprosy. Indian J Dermatol Venereol Leprol 2008;74:174-6.
12. Lienhardt C, Fine PE. Type 1 reaction, neuritis and disability in leprosy. What is the current epidemiological situation? Lepr Rev 1994;65:9-33.
13. Kar HK, Sharma P. Leprosy reactions. In: Kar HK, Kumar B, editors. IAL Textbook of Leprosy. New Delhi: Jaypee; 2010. p. 271.
14. Rao PN, Pratap D, Ramana Reddy AV, Sujai S. Evaluation of leprosy patients with 1 to 5 skin lesions with relevance to their grouping into paucibacillary or multibacillary disease. Indian J Dermatol Venereol Leprol 2006;72:207-10.
15. Shivaswamy KN, Shyamprasad AL, Sumathy TK, Ranganathan C, Agarwal V. Clinico histopathological correlation in leprosy. Dermatol Online J 2012;18:2.
16. Revankar CR, Ganapatì R, Naik DD. Multidrug therapy for paucibacillary leprosy: Experience in Bombay. Indian J Lepr 1985;57:773-9.
17. Dhir R, Guha PK, Singh G. Short term chemotherapy of paucibacillary leprosy. Indian J Lepr 1986;58:549-54.
18. Pavithran K. Relapse of paucibacillary leprosy after short course multidrug therapy. Indian J Lepr 1988;60:225-9.
19. Ramu G. Duration of MDT for paucibacillary leprosy. Indian J Lepr 1992;64:1-7.
20. Goñalves Hde S, Pontes MA, Bührer-Sékula S, Cruz R, Almeida FC, Moraes ME, et al. Brazilian clinical trial of uniform multidrug therapy for leprosy patients: The correlation between clinical disease types and adverse effects. Mem Inst Oswaldo Cruz 2012;107 Suppl 1:74-8.