Comparative study of Uniform-MDT and WHO MDT in Pauci and Multi bacillary leprosy patients over 24 months of observation

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Summary

Study design
An open comparative study between WHO MDT and U-MDT regimen in all types of leprosy over 24 months of observation was carried out at Gandhi Hospital, Secunderabad, India. Periodic assessment of clinical and histopathological parameters at 6 monthly intervals was performed in both groups of patients for grading response to the treatment regimens.

Patients and methods
One hundred and twenty-seven newly diagnosed, untreated leprosy patients classified into PB (≤5 skin lesions) and MB leprosy (>5 skin lesions) were alternately allocated into Study (U-MDT for 6 months) and Control groups (WHO MDT) at entry. Out of the 127 patients included, 64 patients (M-44, F-20; PB leprosy 32 & MB leprosy 32) could be followed-up regularly. These 64 patients were clinically assessed and graded into Good, Moderate and Poor response at 6, 12 and 18 months of the study, and 44 of these patients were also assessed at 24 months of the study. Histopathological assessments were also done at the above intervals.

Results
PB patients
The control and study groups comprised of 14 and 18 patients respectively. When clinical grades were compared, the numbers of Moderate and Good responses were 78% and 61% at 6 months, 86% and 94% at 18 months and 82% and 100% at 24 months in the PB Control and Study groups respectively, suggesting better progressive improvement in the Study group compared to Control group, but the differences were not significant (At 6 months P = 0.2195, at 18 months 0.7305, at 24 months P = 0.3500) Histopathological assessment at 12 months, showed higher percentage of Good responses (100%) in the PB-Study group than in the PB-Control group (86%).

MB patients
The MB Control and Study groups comprised of 22 and 10 patients respectively. In clinical improvement grades, Good responses in the Control group was 36%, 45% and 77% at 12, 18 and 24 months of study, whereas the Study group...
did not have a single Good response at 12 and 18 months with the Poor responses being 50%, 67% and 75% at 12, 18 and 24 months. These differences between the groups were significant at all periods of assessment. (At 12 months $P = 0.0465$, at 18 months $P = 0.0014$, at 24 months $P = 0.0064$). Histopathological assessment showed higher the percentage of Good responses in Control group (100%) compared to Study group (50%) at 18 months.

**Conclusion** U-MDT of 6 months duration was well tolerated and effective in patients with PB leprosy but was too short a regimen adequately to treat patients with MB leprosy.

### Introduction

While recommending multi-drug therapy (MDT) in 1982, the WHO study group divided leprosy patients into Pauci Bacillary (PB) and Multi Bacillary (MB) leprosy for the purpose of therapy. WHO recommended a MDT regimen of two drugs (MDT-PB) and a MDT regimen of three drugs (MDT-MB) for PB and MB patients respectively. However, the definition of PB and MB groups as well as the duration of treatment recommended has been changing over the last 25 years.

**UNIFORM MDT FOR ALL PATIENTS**

The WHO Technical Advisory Group (TAG), in its third meeting in 2002, proposed that a uniform MDT regimen (U-MDT) of 6 months duration should be considered to treat all types of leprosy. The group felt that with WHO MDT being widely implemented with very low relapse rates and complete absence of emergence of *M. leprae* resistance, further shortening and simplification of the MDT regimen by introducing uniform MDT would lead to better sustainability of services after integration. WHO, in its sixth meeting of TAG, proposed the implementation of the project to demonstrate the usefulness of a single short treatment regimen for all cases of leprosy as it has major operational and cost benefits. PB leprosy patients constitute the substantial majority of these cases and the main issue to be addressed for them is one of acceptability and can be tackled in an open study design.

In the present study, we have applied such a protocol of a uniform multi-drug therapy (U-MDT) regimen containing three drugs – dapsone, clofazimine and rifampicin – of 6 months duration for all patients with leprosy. The study assessed the efficacy of the U-MDT regimen based on clinical and histological parameters and compared it with the existing MDT-PB and MDT-MB regimen. The study also attempted to assess the acceptance and compliance of such a regimen.

### Patients and methods

The detailed protocol of the study was submitted to the Human Ethics Committee of Gandhi Hospital, Secunderabad, India and clearance was obtained. One hundred and twenty seven consecutive untreated leprosy patients attending the Department of Dermatology & Leprosy at Gandhi Hospital between March 2003 and July 2005 were included in the study.

Patients of both sexes between the ages of 10 and 60 years were included. Pure neuritic leprosy patients, patients on long-term steroid therapy, patients with associated systemic...
cases of tuberculosis or other chronic diseases and pregnant and lactating women were excluded from the study. Informed written consent was taken from all patients before enrollment. Patients of PB and MB leprosy were allocated alternately into Study and Control groups. Both PB and MB patients of the Study group were given U-MDT drug regimen (dapsone 100 mg daily, clofazimine 50 mg daily and rifampicin 600 mg once a month, for 6 months). Whereas patients of PB Control group were given WHO MDT-PB for 6 months and patients of MB Control group were given WHO MDT-MB for 12 months.

CASE DEFINITIONS

**Pauci-bacillary (PB) leprosy:** Leprosy patients with five or less than five skin lesions. (Satellite lesions were counted as a part of the parent skin lesion).

**Multi-bacillary (MB) leprosy:** Leprosy patients with more than five skin lesions.

The total number of patients included in the study was 127 (Male 83; Female 34). Patient information and details of clinical examination were recorded and body charting done at initial registration and at the end of the study. Disabilities and adverse effects of drugs were recorded.

INVESTIGATIONS AND FOLLOW-UP

Patients were followed up for a minimum period of 18 months, and a maximum of 24 months after enrollment and periodic clinical assessments for changes in disease activity were made at 6 monthly intervals. To encourage patients to attend the follow-up clinic ‘Reminder postcards’ were posted to their residential addresses every 6 months. Skin smears were taken from three sites in all patients at entry, 12 and 24 months and stained with Ziehl Nelsen’s stain. Acid Fast Bacilli (AFB) were looked for and Bacterial Index (BI) of smears was graded by Ridley’s scale. The highest BI observed of the three sites was taken as the BI of the patient. Skin biopsies were taken at the time of entry, 6 months, 12 months, 18 months and 24 months. All the skin biopsies were taken from the same representative lesion selected in each patient at the beginning of the study. Biopsies were processed and stained with H&E and modified Fite stain. Patients with leprosy reactions (I & II) were hospitalised whenever necessary and treated with prednisolone and other measures without increasing the dose of clofazimine.

CLINICAL ASSESSMENT

**Clinical scoring system for PB group:** The following scoring system as shown in Table 1 was adopted in this study which was based on the methodology followed by the ‘2–3 multi lesion

| Table 1. Clinical scoring system for PB patients |
|-----------------------------------------------|
| Clinical Parameter | None | Mild | Moderate | Marked |
| Hypopigmentation | 0 | 1 | 2 | 3 |
| Erythema | 0 | 1 | 2 | 3 |
| Infiltration | 0 | 1 | 2 | 3 |
| Appearance of lesion | 0 (Not visible) | 1 (Doubtful) | 2 (Faintly visible) | 3 (Clearly visible) |
| Hypo/Anaesthesia | 0 (No loss) | 1 (Doubtful) | 2 (Definite loss) | 3 (Complete loss) |
multicentre trial group’ of 2001 and its modified version followed in a study based at Mumbai in leprosy patients with one to three skin lesions.

We have included only five clinical parameters compared to six parameters followed in the above studies. The parameters, hypopigmentation, erythema, infiltration and appearance of lesions were judged on a visual scale of 0 to 3. All assessments were done by the same clinician (PNR). The maximum possible clinical score was 15 at entry of the patient into the study. All PB patients were assessed at entry, at 6, 12 and 18 months and wherever possible at 24 months.

As this open study was a part of the PhD work of the lead author (PNR), it was necessary that he be involved in all clinical assessments of the patients and was not blinded to the treatment regimen given to patients. However, to minimise bias, these clinical assessments were validated by another clinician (DVSP) blinded to the treatment regimen received by the patients.

Clinical grading of outcome in PB groups: The patient was said to have ‘Good improvement’ if there was more than 70% reduction in the total clinical score, compared to the score recorded at entry, ‘Moderate improvement’ when there was a 30 to 70% reduction in clinical score and ‘Poor improvement’ when there was less than 30% reduction in the total clinical score.

Clinical assessment system for MB groups: The scoring system mentioned for the 1–5 lesion group was not applicable to patients with multiple skin lesions of the MB group. A literature search did not find a clinical scoring system for MB patients; hence a new scoring system was devised. The patient was assessed based on three clinical parameters; number of skin lesions, size of the lesions and presence of infiltration in the lesions. The BI of skin smears could not be considered as a parameter for assessment of improvement, as the majority of MB patients were negative for AFB in skin smears. All the MB patients in the study were assessed at entry, at 12 and 18 months and, wherever possible, at 24 months.

Clinical grading of outcome in MB group: The definition of two groups of ‘improved’ or ‘not improved’ for each parameter is mentioned in Table 2.

Good improvement: Defined as improvement in all three parameters. Moderate improvement: improvement in two out of three parameters. Poor improvement: improvement in only one out of three parameters.

HISTOPATHOLOGICAL ASSESSMENT

Skin biopsies were taken at the time of entry, 6 months, 12 months, 18 months and 24 months from all the patients in the study. All slides were randomly assessed without grouping to prevent bias. The histopathologist (SS), who was blinded to the clinical details, examined and graded all the sections. All sections were assessed based on the cellularity of

| Parameter          | Not improved                  | Improved      |
|--------------------|-------------------------------|---------------|
| No. of skin lesions| Same or Increased             | Reduced       |
| Infiltration       | Present                       | Absent        |
| Size of lesions    | Same or Increased             | Decreased     |

Table 2. Clinical scoring system for MB patients
the granuloma, evidence of dermal oedema and involvement of dermal nerves. Granuloma fraction\(^3\) (GF) was assessed visually and recorded. Fite stained sections were graded for Bacterial Index of granuloma (BIG). Histologically the sections were classified according to Ridley-Jopling.\(^6\)

The biopsies taken at stated intervals were compared for changes in disease activity based on histological parameters to assess the efficacy of treatment. The parameters on which the assessment was based were: changes in the cellularity of the granuloma including dermal oedema, GF, BIG and histological classification. The follow-up biopsies were compared to the histopathology at entry and graded, based on these four parameters as Good improvement, Reversal Reaction (RR), No change and Poor improvement/Deterioration, as shown in Table 3.

At the end of the study the clinical outcome grades of patients were read along with the histological outcome of skin biopsies to arrive at the final assessment.

**STATISTICAL METHODS**

Data was analysed with independent two sample student t test for significance of difference with the help of SPSS soft ware version 10.

**Results**

Out of the 127 patients originally included, 63 patients became ineligible for continuation in the study within the first 12 months of the study period. Reasons for their exclusion from the study were: taking additional drugs, taking drug therapy for longer than advised, irregular follow-up due to change of residence or work place, and other personal reasons. The remaining 64 patients constituted the ‘Study Cohort’ whose results are presented. All 64 were followed and assessed at 6, 12 and 18 months of the study and 44 of these patients could be assessed at 24 months of the study.

### Table 3. Histopathological grading of improvement in follow-up biopsies

| Grades of Improvement/Changes | Cellularity of granuloma | Granuloma fraction (GF) | BIG | Histological classification |
|------------------------------|--------------------------|-------------------------|-----|-----------------------------|
| Good improvement             | Lymphocytes: same or Decreased | Decreased | Same or decreased | Upgrading towards TT |
|                              | Macrophage: same or decreased | | | |
|                              | Epitheloid cells: same or decreased | | | |
|                              | Increase in dermal edema, | | | |
|                              | Lymphocytes, Epitheloid, | | | |
|                              | and Giant Cells | | | |
| Reversal reaction            | Increased | Same or increased | Same or upgraded |
| No improvement/change        | No change | Same | Same Downgrading towards LL |
| Poor improvement/            | Increase in cellularity with increased Lymphocytes and Macrophages | Same | Same |
| Deterioration                | | Increased | | |

When, three out of four histological parameters demonstrate the desired effect, it is to be considered to have conformed to the expected result.

BIG = Bacterial index of Granuloma, TT = Tuberculoid leprosy, LL = Lepromatous leprosy.
Table 4. Numbers of patients in study and control groups

| Patient group | Study group | Control group | Control group |
|---------------|-------------|---------------|---------------|
|               | On U-MDT | MDT-PB for 6 months | MDT-MB of 12 months |
| PB patients (32) | 18 | 14 | – |
| MB patients (32) | 10 | – | 22 |

PB = Pauci bacillary, MB = Multi bacillary, U-MDT = Uniform MDT, MDT = Multi drug therapy.

DETAILED STUDY AND CONTROL GROUPS OF PB AND MB PATIENTS

In the Study Cohort of 64 patients, 32 were PB patients and 32 MB patients (Male: 44 Female: 20). The prior allocation of these patients to the Control and Study groups is shown in Table 4.

In the PB patients, Study and Control groups contained 18 and 14 patients respectively. In the MB patients, the Study group contained only 10 patients compared to 22 in the Control group. The disproportionate numbers between the Study and Control groups was due to large number of dropouts in the Study group on U-MDT in the first year of the study for taking additional drugs.

Clinical types in PB and MB groups: When patients under study were clinically typed based on the Ridley-Jopling classification, (Table 5), BT patients were 11 out of 14, and 10 out of 18 in PB Control and Study groups respectively. In the MB Control and Study groups, BB, BL & LL patients together were 17 out of 22 and 9 out of 10 respectively.

SKIN SMEARS

At entry, all the 11 smear positives were in MB patients, with six patients in the MB Control and five patients in the MB Study group. The BI ranged from 1 † to 4 † with three patients having BI values of 3 †. None of the patients with negative smears at entry showed positive smears subsequently. In the follow-up skin smears, five patients remained positive at 12 months and two patients at 24 months and their BI was not higher than the value at the time of entry.

CLINICAL AND HISTOPATHOLOGICAL ASSESSMENT

Out of 64 patients included in the study, biopsies of 87% of patients were available for histological assessment at entry, of 45% at 12 months, of 21% at 18 months and of 10% of

Table 5. Clinical classification according to Ridley-Jopling in the PB & MB groups

| Classification | PB Control Group | PB Study group | MB Control group | MB Study group |
|----------------|------------------|----------------|------------------|----------------|
| TT             | 3                | 8              | –                | –              |
| BT             | 11               | 10             | 5                | 1              |
| BB             | –                | –              | 3                | –              |
| BL             | –                | –              | 6                | 5              |
| LL             | –                | –              | 8                | 4              |
| Total          | 14               | 18             | 22               | 10             |

TT = Tuberculoid leprosy, BT = Borderline tuberculoid leprosy, BB = Borderline borderline leprosy, BL = Borderline lepromatous leprosy, LL = Lepromatous leprosy, PB = Pauci bacillary, MB = Multi bacillary.
patients at 24 months. By contrast the number of patients available for clinical assessment was 100% at 12 and 18 months and 69% at 24 months.

**Observations in PB Control and Study Group of Patients Over 24 Months**

*Comparisons of clinical improvement grades*

The clinical grades at the various study intervals in the PB groups are shown in Table 6. At 6 and 12 months of assessment, the numbers of Moderate and Good grades were higher (78% & 86%) in PB Control group compared to the PB Study group (61% & 78%). However, by 18 and 24 months, the Moderate and Good grades were higher (94% & 100%) in the PB Study group compared to the PB Control group (86% & 82%), suggesting greater improvement in the PB Study group but the differences were not significant (At six months $P = 0.2195$, at 12 months $P = 0.4656$, at 18 months $P = 0.7305$ and at 24 months $P = 0.3503$).

*Comparisons of histopathological improvement grades*

When the histopathological grades were compared between PB Study group and PB Control group (Table 7), the percentage of Good grades (including RR) for PB Study group were 91%, 100%, 83% and 100% at 6, 12, 18 and 24 months compared to 80%, 86%, 100% and 67% for PB Control group. These results should be considered with caution, as the number of skin biopsies was very small and statistical methods could not be applied.

**Observations in MB Control and Study Group of Patients Over 24 Months**

*Comparisons in clinical improvement grades*

In MB patients, all 22 patients of Control group were clinically graded at 12 and 18 months of follow-up, however, by 24 months only 17 patients were available for assessment.

| Groups        | Improvement | At 6 months | At 12 months | At 18 months | At 24 months |
|---------------|-------------|-------------|--------------|--------------|--------------|
| PB Control group | Good        | 2/14 (14%)  | 2/14 (14%)  | 6/14 (43%)  | 6/11 (52%)   |
|               | Moderate    | 9/14 (64%)  | 10/14 (72%)  | 6/14 (43%)  | 3/11 (27%)   |
|               | Poor        | 3/14 (22%)  | 2/14 (14%)  | 2/14 (14%)  | 2/11 (18%)   |
| PB Study group | Good        | 5/18 (28%)  | 5/18 (28%)  | 8/18 (44%)  | 7/9 (78%)    |
|               | Moderate    | 6/18 (33%)  | 9/18 (50%)  | 9/18 (50%)  | 2/9 (22%)    |
|               | Poor        | 7/18 (39%)  | 4/18 (22%)  | 1/18 (6%)   | None         |
| MB Control group | Good        | –           | 8/22 (36%)  | 10/22 (45%) | 13/17 (77%)  |
|                | Moderate    | –           | 10/22 (45%) | 11/22 (50%) | 3/17 (17%)   |
|                | Poor        | –           | 4/22 (19%)  | 1/22 (5%)   | 1/17 (6%)    |
| MB Study group | Good        | –           | None        | None        | 1/4 (25%)    |
|                | Moderate    | –           | 5/10 (50%)  | 2/6 (33%)   | None         |
|                | Poor        | –           | 5/10 (50%)  | 4/6 (67%)   | 3/4 (75%)    |
In the Study group, all 10 patients were graded at 6 and 12 months. However, by 18 months, the Study group was reduced to six patients, because four patients were transferred to WHO MDT-MB therapy due to poor response to treatment, details of which is given in Table 8. At 24 months, only four out of these six patients were available for clinical assessment. A comparison of the clinical grades of response between the Control and Study group is given in Table 6. The percentages of Good grades were consistently higher in the Control group at 12, 18 and 24 months of study (36%, 45% and 77%) whereas the Study group did not have a single Good grade at 12 or 18 months. More importantly, the percentage of Poor grades in the Study group was 50%, 67% and 75% at 12, 18 and 24 months respectively. The differences in clinical improvement grades of Control and Study groups at 12 months, 18 months and 24 months, were highly significant (At 12 months $P = 0.0465$, at 18 months $P = 0.0014$, at 24 months $P = 0.0064$).

Comparisons of histopathological improvement grades

A comparison between the Control and Study groups is presented in Table 7. The percentage of Good grades (including RR) in the Control group was 77% and 100%, at 12 and 18 months compared to 100%, and 50% in the Study group. However, the numbers were too few for statistical comparisons.

Table 7. Histopathological improvement grades in PB and MB groups of patients at stated intervals

| Groups         | Improvement         | At 6 months | At 12 months | At 18 months | At 24 months |
|----------------|---------------------|-------------|--------------|--------------|--------------|
| PB Control group | Good/RR             | 4/5 (80%)   | 6/7 (86%)    | 1/1 (100%)   | 2/3 (67%)    |
|                | No Change/Poor      | 1/5 (20%)   | 1/7 (14%)    | None         | 1/3 (33%)    |
| PB Study group  | Good/RR             | 10/11 (91%) | 9/9 (100%)   | 6/6 (83%)    | 1/1 (100%)   |
|                | No Change/Poor      | 1/11 (9%)   | None         | None         | None         |
| MB Control group| Good/RR             | –           | 7/9 (77%)    | 12/12 (100%) | 6/6 (100%)   |
|                | No Change/Poor      | –           | 2/9 (23%)    | None         | None         |
| MB Study group  | Good/RR             | –           | 4/4 (100%)   | 1/2 (50%)    | –            |
|                | No Change/Poor      | –           | None         | None         | None         |

RR: Reversal reaction. Note: In Skin biopsy, 3 patients in PB Control group showed RR at 12 months and 1 patient each of PB Study group showed RR at 6, 12, and 18 months. In MB Control group 1 patient showed RR at 18 months and in MB Study group 1 patient showed RR at 12 months.

In the Study group, all 10 patients were graded at 6 and 12 months. However, by 18 months, the Study group was reduced to six patients, because four patients were transferred to WHO MDT-MB therapy due to poor response to treatment, details of which is given in Table 8. At 24 months, only four out of these six patients were available for clinical assessment. A comparison of the clinical grades of response between the Control and Study group is given in Table 6. The percentages of Good grades were consistently higher in the Control group at 12, 18 and 24 months of study (36%, 45% and 77%) whereas the Study group did not have a single Good grade at 12 or 18 months. More importantly, the percentage of Poor grades in the Study group was 50%, 67% and 75% at 12, 18 and 24 months respectively. The differences in clinical improvement grades of Control and Study groups at 12 months 18 months and 24 months, were highly significant (At 12 months $P = 0.0465$, at 18 months $P = 0.0014$, at 24 months $P = 0.0064$).

Comparisons of histopathological improvement grades

A comparison between the Control and Study groups is presented in Table 7. The percentage of Good grades (including RR) in the Control group was 77% and 100%, at 12 and 18 months compared to 100%, and 50% in the Study group. However, the numbers were too few for statistical comparisons.

Table 8. Clinical details of MB patients on U-MDT who were shifted to WHO MDT-MB

| Pt. No | Age | Sex | Diagnosis | No. lesions | Histo Diag | BL | Clinical grade at 12months | Clinical grade at 18 months |
|--------|-----|-----|-----------|-------------|------------|----|----------------------------|----------------------------|
| 56     | 35  | F   | BL        | > 30        | BT         | (−) | Poor                       | Poor                       |
| 110    | 60  | M   | LL        | > 30        | LL         | 3+  | Poor                       | Poor                       |
| 114    | 50  | F   | BT        | > 10        | BL         | (−) | Poor                       | Poor                       |

Pt. No: patient registration number, MB = Multi bacillary, BT = Borderline tuberculoid, BL = Borderline lepromatous, LL = Lepromatous leprosy, U-MDT = Uniform Multi drug therapy.
LEPROSY REACTIONS, ADVERSE EFFECTS OF DRUGS AND TOLERANCE TO THERAPY

Leprosy reactions

At the time of entry, out of 64 patients, 10 (1 BL and 9 TT or BT) patients presented in Type 1 reaction and two (1 BL and 1 LL) patients had Type 2 reaction. The Type 1 reactions were mild to moderate in intensity and there was associated motor weakness in one patient. During the first 12 months of follow-up, a further 10 patients developed Type 1 and three patients developed Type 2 reactions. One MB patient with Type 1 reaction at entry developed Type 2 reaction after 6 months of therapy. Between the 18 to 24 months of observation, new Type 1 reactions were observed in three patients. No correlation between reactions and treatment groups could be observed.

Adverse effects of drugs

During the study two patients developed ‘Dapsone Hypersensitivity Syndrome’ (DHS) and one patient developed ‘Acute Generalized Exanthematous Pustulosis’ (AGEP) to Dapsone. They occurred during the first four weeks of therapy and were managed appropriately. As all these occurred in PB patients, Dapsone was substituted with Clofazimine.

Tolerance to therapy

Barring these adverse effects, the drug therapy was generally well tolerated. Clofazimine pigmentation was observed in 11 patients. Of these, two were PB and remaining nine MB patients. In the two PB patients who developed skin pigmentation, it was marked at the periphery of the skin lesions giving them an annular configuration. In both these patients the pigmentation regressed over a period of 9 months.

Discussion

It the year 2002, the WHO TAG on elimination of leprosy reported on the need to consider a uniform MDT (U-MDT) regimen of MDT-MB of 6 months duration to treat all types of leprosy irrespective of clinical classification. The report suggested that ‘such a uniform regimen will promote easier logistic support, simpler information system, reduced training needs and thus provide better sustainability through integration’. However, there is yet no evidence from any controlled clinical trials, even of a limited nature, to support this shortening of duration of the treatment to 6 months. The TAG in 2003 came out with the basic protocol and proposed that it be implemented for all cases of leprosy.

Some workers expressed concern regarding the proposed implementation of U-MDT, who felt that U-MDT of 6 months will over-treat PB leprosy patients and under-treat MB patients, especially those with a high initial BI. Others felt that there were still serious concerns regarding the efficacy of a 12 month MDT regimen for MB leprosy and that there was no justification for shortening the duration to 6 months.

The U-MDT trial by WHO was launched in September 2003, with the participation of four districts in India and three districts in China with the National Institute of Epidemiology (NIE), Chennai, India as the international coordinating center. The study set out to assess the
efficacy and effectiveness of the U-MDT regimen for all types of leprosy under routine field conditions on the basis of clinical response and complications. It has an open study design and is not a comparative study. The emphasis is on close monitoring of patients during treatment and the long-term indicator for assessing the effectiveness of U-MDT is the cumulative relapse rate at the end of 5 years after completion of treatment. The total number of patients enrolled as of April 2006 was 2507. Of these, 2106 patients (84%) have completed the treatment phase. Preliminary observations from the study are that patients opted and accepted U-MDT regimen in all the participating centres. At the time this paper was being compiled, the key results of the trial are still awaited. Studies on U-MDT have also been initiated at a few other centres around the world for example in Bangladesh and Brazil, where the enrollment of patients has been completed and the results are awaited.

The present study is a hospital based open comparative study between U-MDT regimen and WHO MDT regimen in all types of leprosy over 24 months of observation. Periodic assessment of clinical and histopathological parameters at 6 monthly intervals was performed in both groups of patients for grading response to the treatment regimens. Patients came from in and around the twin cities of Hyderabad and Secunderabad, India. The high percentage of dropouts (about 50%) from the study groups could be attributed to the nature of the population, which included a significant number of migrants from the neighbouring districts.

PB patients on U-MDT in the present study showed marginally better clinical grades compared to PB patients on WHO MDT-PB, although the differences were not significant. Two similar comparative studies were conducted on PB patients, with one group getting clofazimine for 6 months in addition to the standard WHO MDT-PB. Both these studies concluded that the patient group with the addition of clofazimine fared better, although the parameters considered were different. The JALMA study was a clinical study whereas the Tamil Nadu study was based on clinical and histopathological parameters. The JALMA study reported that in 20 of the 125 patients in the control group (on WHO MDT-PB) and in 10 of 133 patients in Study groups (with the addition of clofazimine) the disease was active and that the difference between these observations was statistically significant when followed up for 2-5 to 3-5 years. The authors concluded that the addition of clofazimine to the PB treatment regimen is an improvement over the available treatment schedule and it has the added advantage of being operationally more easily administered in the field. The comparative study from Tamil Nadu recorded clinical inactivity in 12 out of 22 patients on PB MDT whereas inactivity was observed in 16 out of 22 patients with addition of clofazimine, at 12 months of observation. Similar observations were made in the present study with the PB Study group on U-MDT containing clofazimine showing better grades overall and continued higher response at 18 and 24 months compared to PB study group who were on WHO MBT-PB. This continued favourable response could be attributed to the depot action of the clofazimine in the tissues.

The report of the eighth WHO TAG on Leprosy Control in 2006, mentioned that in the ongoing trial on U-MDT, there were no difficulties with respect to pigmentation due to clofazimine in PB patients. The study at JALMA observed that in India there is not much of a problem regarding the acceptability of clofazimine. Similar observations were made in the present study with all PB patients accepting and tolerating clofazimine very well.

MB patients are a heterogeneous cluster, although they are grouped together for treatment purpose. They have a sub-group of BL and LL patients with high initial BI and multiple skin lesions and also BT patients who are smear negative with 6 to 10 skin lesions. This is one of the important reasons why the method of clinical scoring system applicable to PB patients
was found not useful for MB patients. With no tested scoring system readily available for MB patients, we have devised and followed a clinical scoring system in the present study wherein three clinical parameters (number of skin lesions, presence of infiltration and size of the skin lesions) were assessed and recorded. These three parameters were chosen after much debate, among other clinical parameters associated with MB leprosy. They were found to be relevant to all types of patients of MB leprosy.

In the present study, it was observed that MB patients on U-MDT, showed a significantly poor response at all periods of clinical assessment at 12, 18 and 24 months compared to the patients on WHO MDT-MB. The response was so poor in four of the patients on U-MDT that they were shifted to WHO MDT-MB at 18 months of observation (Table 8). The number of skin lesions in these patients at entry was more than 10, with three of them presenting with more than 30 skin lesions. Two of these patients were skin smear positive with a BI of 3. Three of these patients also had associated type 1 reaction between 6 and 12 months of observation. In all four patients, new lesions were observed during follow-up along with persistence of old lesions at 18 months of study with clinical grades of assessment being poor. The skin smears continued to be positive in both the patients. It was concluded that U-MDT was not adequate for these patients and WHO MDT-MB of 12 months was re-instituted at 18 months of observation, after discussion with the medical officer of the leprosy clinic.

Statistical analysis of histopathology observations was not possible because of the small number of skin biopsy results. Other longitudinal clinico-histopathological studies have had similar experiences. In a comparative study of PB patients who were given either ROM (rifampicin, ofloxacin and minocycline) or MDT-PB, the number of patients enrolled and evaluated clinically were 51, whereas only 14 skin biopsies were available for histopathological evaluation.17 In a clinico-histological study where 30 patients were recruited into the study,18 at 12 months only 20 skin biopsies and at 18 months only four skin biopsies were evaluated. It is observed that in many longitudinal studies of importance, skin biopsy is not included in the evaluatory criteria and conclusions are drawn on the basis of clinical findings alone.4,14,19 One of the strengths of the present study was the combination of clinical and histopathological tools to assess improvement during follow-up.

Results of studies, including a WHO trial, involving U-MDT are not yet available to compare with the present study. However, it is important to note that the WHO trial is not a comparative trial of U-MDT and WHO MDT regimen.

There have been reports of high rates of relapses in the high BI and multiple skin lesion groups of patients even with 12 and 24 months of MDT-MB regimen.20,21 Others express caution regarding reducing the duration of the MDT-MB in MB patients recognising the problems of persisters and relapses even with the 24-month regimen.22,23 The risk of over diagnosis of MB relapse does exist but it is probably not very high if one follows proper procedures and criteria. On the other hand the risk of under diagnosis of MB relapse might be much greater, because of ignorance, poor quality of skin smears, and insufficient duration of follow-up or combination of all these.22

Clearly there are grounds for concern regarding the reduction of the duration of treatment for MB patients from 24 to 12 months. As there are several reports of relapses in MB patients on MDT-MB of 24 & 12 months duration, further shortening of the duration to 6 months should be considered with great caution and only if it is found to be as effective as the present regimen of 12 months. Mere acceptability factor of the U-MDT regimen cannot be sufficient for its routine implementation in the general health services.
In conclusion, U-MDT was observed to be an effective and useful regimen to treat PB patients of leprosy. However, in MB patients it was not found to be an effective regimen when compared to WHO MDT-MB of 12 months duration.

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