PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	6 months fixed duration multidrug therapy in paucibacillary leprosy: Risk of relapse and disability in Agra PB cohort study
AUTHORS	KUMAR, ANIL ; GIRDHAR, ANITA; Girdhar, Bhavneswar

VERSION 1 - REVIEW

REVIEWER	Maria Leide W. de Oliveira Medical school/Federal University of Rio de janeiro-Brazil I have no conflict of interest
REVIEW RETURNED	07-Jun-2012

THE STUDY	1-The authors intend to evaluate the long term outcome of fixed duration MDT (MDT_U) for Paucibacillary (PB) leprosy in a prospective study in field condition. It means a study of efficacy, but in fact is a study of effectiveness/efficiency . 2-The first paragraph of the abstract " low relapses after MDT in PB leprosy led to recommendation of reducing therapy to 6 months". That is not correct . PB leprosy does not have its treatment duration shortened by MDT-U. The current standard MDT for PB leprosy is just recommended to be for 6 months and it is successful . Therefore, MDT-U is an innovation only for Multibacillary (MB), according to the treatment duration. 3-In the inclusion/exclusion criteria, the authors mentioned that all cases are diagnosed utilizing field classification recommended by WHO, based only on clinical examination of patients and no laboratory procedure was referred. However, in the results skin smears was mentioned. Were all patients submitted to skin smears? There was a noticeable difference if this exam was considered to classify patients in both Multibacillary(MB)or Paucibacillary (PB) kind of leprosy 4-The limitations of the study design were not mentioned. Of course to evaluate it properly, it is necessary to have a control PB group receiving standard MDT. If the authors also followed PB patients receiving standard MDT could the use of nested-cohoort make the study more robust.
RESULTS & CONCLUSIONS	1-The results are clear but only present a descriptive study of MDT-U applied to PB cases in a very well accompanied treatment cohort.

	It is a useful operational research for control program use, to answer relapse rate and disability occurrence after MDT-U treatment. 2-It was not clear if the slight skin smear was utilized or not for the classification. 3- One interesting aspect to be focused on the discussion is the validation of the clinical operational classification as only few patients presented positive smears. 4-What is new in MDT-U for PB leprosy? Drug tolerance and patient acceptance, as the patients will receive one more drug comparing to the standard MDT. This increase both the costs and side effects of this regimen for PB. Otherwise, could it increase its efficacy, mainly against dapsone resistance, which could be measured by clinical status after cure and relapse rate. Also, the variable reaction could be compared, as the MDT-U adds Clofazimine), which has an inflammatory effect. It could influence the level of disability of patients treated. The low rate of disability was also mentioned in the discussion, however, without mention to a possible clofazimine effect in the reaction reduction. 5-Another question referred to in table 1, in a classification of clinical status: TT, BT BTR: I am not sure if it is scientifically accepted that this kind of classification could be done without histopatologic exam. Even recognizing the diagnostic accuracy of the experienced leprologist Clinical status: The abbreviation and definition was not presented in table 1 6-The statistical results should be linked to the results in the tables. 7-The discussion is poor. The main advantages and disadvantages for giving MDT-U to PB leprosy were not emphasized

REVIEWER	Sinesio Talhari Institute of Tropical Medicine Manaus, Am, Brazil
REVIEW RETURNED	14-Jun-2012

GENERAL COMMENTS	The criteria for classification and leprosy diagnosis adopted by the authors in this trial are those defined by the World Health Organization (WHO). Patients were classified according to the number of lesions and the diagnosis was based on clinical aspects and impairment or loss of sensations (tested with ball point pen) and/or one thickened nerve. According to the WHO, baciloscopy or histopathology are not necessary for leprosy diagnosis. However, for the large majority of leprologists and dermatologists (Diana N.J Lockwood, Sujai Sunnetha - Leprosy: too complex a disease for a single elimination paradigm Bulletin WHO, March 2005), sensation tested with a ball point pen is not the best approach for the confirmation of leprosy diagnosis. Additionally, anxious patients and children could give wrong answers when tested for sensation. Bacilloscopy and mainly histopathology are important tools to confirm leprosy diagnosis especially in a trial in which the main goal was the risk of leprosy relapse.

	Another difficult clinical aspect is to define if a patient has a thickened nerve or not. Divergence among leprologists is relatively frequent and electroneuromiography (ENM) is very important in doubtful patients. Of course this diagnostic approach is not feasible for field work but it is very important in trials, to confirm if the supposed thickened nerve is really impaired or not. Over 40% of the patients had thickened nerves but It was not possible to find in the manuscript which were the most frequently affected nerves and how many patients had only thickened nerves and no cutaneous lesions. This is an interesting aspect because of the low incidence of disabilities. With such a high number of patients with thickened nerves it was expected to observe a higher number of patients with disabilities. May be in some of this patients ENM could be helpful in order to avoid the possibility of wrong diagnosis. In most of WHO reports the efficacy of MDT for paucibacillary leprosy is over 98%. The lowest efficacy observed by the authors was probably related to the diagnosis criteria and difficulties in differentiate between reactions, relapse, regression of cutaneous lesions and changes in sensation. The references are not sufficient. Very important and recent WHO Technical Reports about the efficacy and other aspects related to MDT are not listed and discussed in the manuscript. WHO data are based on countries report but are based on the experience with MDT in millions of patients, since 1982. The mentioned aspects deserve more discussion by the authors.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1 (Maria Leide W. de Oliveira0

1. Sorry , We only intend to assess the long term effects of 6 months Fixed duration treatment as recommended by WHO. It is not Uniform MDT (MDT-U) as understood by the respectable reviewer.
2. In view of above clarification (1), this is not true. We are only meaning as the treatment for PB leprosy was shortened from 12 to 6 months in 1995 by WHO.
3. Yes, skin smears was taken but all never cooperate in the field setting, so only those who cooperated gave the permission to take skin smear. Only 2 patients were 1+ -low positivity so did not give much weightage.
4. We followed all the patients given 6 months PB-MDT as a cohort. Reassessed every 6 months for first few years and then annually to assess for relapse, reaction, disability etc.
5. Clinical status is bases on lesions presentations and was done by very long experienced Leprologists /dermatologist with 15-30 years clinical experience. Histology in field conditions is really a difficult one and thus was not attempted. Abbriviations are added in Table 1.
6. If there was limited linkage, it is now extended with tabulated data.
7. Discussion has been extended in view of the comments and WHO reference.

Reviewer 2 (S. Talhari)

1. I agree that “ball point pen testing is not the best method” to diagnose leprosy as it is dependent on pressure applied. However it is accepted as functional approach worldwide. Histology is a difficult preposition under field conditions and skin smear is agreed upon by many patients. Since we have well qualified and long experienced Leprologists, diagnosis is very well done based on lesion, presence of anesthesia, thermal temperature, morphology of lesion etc.

2. All the main nerves (ulnar, median, radial, lateral popliteal, Post tibial, and facial)were palpated and based on this , only affected nerves of the confirmed patients were recorded.
3. The details of thicken nerves are given in the text.
4. Many studies have shown that risk of disabilities is higher when more nerves are involved. Since in this study none of the patients has more than 1 nerve (many had only cutaneous nerves) so probably the risk has been lower.
5. It is true that many patients who do not have palpable nerves do develop disability at later stage. A study based on Electrophysiology has suggested that many might have silent neuropathy (without symptoms) but such studies are difficult in field settings and more so when field setting is more 100 KM away from institutions where this could be possible. However, a well planned study in now under way (as TENLEP study - multicentric) and hopefully will open new box of knowledge.
6. One of the reasons of low relapses and high cure in WHO based reports is that it is based on data reported from programme conditions. Where probably, many things are assumed and may not have been observed. For example; once 6 months MDT is given to a patient, the patient is assumed to be cured. This may however be not true if observe properly and closely. We have followed up patients regularly. Such similar conditions make the difference on observations.
7. The discussion is now added.

VERSION 2 – REVIEW

REVIEWER	Maria Leide W. Oliveira,MD,Phd Medical School/Federal Universuty of Rio de Janeiro-Brazil I consider this article could be accepted after essential revision. I declare that I have no competing interests on this.
REVIEW RETURNED	09-Jul-2012

THE STUDY	Abstract: the first paragraph of the abstract (first revision) " low relapses after MDT in PB leprosy led to recommendation of reducing therapy to 6 months". The same paragraph in the second revision: Abstract: " Low relapses after 12 months multidrug therapy in paucibacillary (PB) leprosy led to recommendation of reducing therapy to 6 months." R-As I mentioned below, in my first revision. PB leprosy does not have 12 months treatment officially recommended neither its treatment duration shortened by MDT-U, the recent innovation recommended by WHO. PB leprosy does not have its treatment duration shortened since the beginning of MDT. The current standard MDT for PB leprosy is just recommended to be for 6 months and it is successful . More recently, MDT-U this reduction but only for Multibacillary (MB), according to the treatment duration. So the authors could only refer that many studies focused on MDT for MB and rarely on PB…….. Methodology: in the inclusion/exclusion criteria, the authors mentioned that all cases are diagnosed utilizing field classification

	recommended by WHO, based only on clinical examination of patients and no laboratory procedure was referred. However, in the results skin smears was mentioned. Were all patients submitted to skin smears? Not answered. -There was a noticeable difference if this exam was considered to classify patients in both Multibacillary(MB)or Paucibacillary (PB) kind of leprosy . -Another question referred to in table 1, in a classification of clinical status: TT, BT BTR: I am not sure if it is scientifically accepted that this kind of classification could be done without histopatologic exam. Even recognizing the diagnostic accuracy of the experienced leprologist. At least a mention to this aspect should be done. -The limitations of the study design were not mentioned
RESULTS & CONCLUSIONS	The results are clear but they only show a descriptive study of MDT, applied to PB cases in a very well accompanied treatment cohort. It is a useful operational research for control program use, to answer relapse rate and disability occurrence after treatment. One interesting aspect to be focused on is the validation of the clinical operational classification, as only few patients presented positive smears. Despite continuously referring to this shortening in this second version, which I´ve never read in WHO documents, since the first WHO MDT recommendation for PB leprosy, I understood that the study subject is the evaluation of the standard PB /MDT, which should be mentioned in the Methods item.

VERSION 2 – AUTHOR RESPONSE

Thank you for very useful comments and following corrections as suggested are done.

1. The sentence in abstract has been modified as suggested by reviewer.
2. The skin smear was to be attempted for all patients but many patients under field conditions do not agree for skin smear as it involves a cut at 1 or more sites and results in bleeding. However we did not insist on skin smear once patient disagreed and patients were treated as per clinical classification.
3. The clinical classification as I/TT/BT is based on clinical presentation of lesions. Although histopathology is certainly useful but could not be done in field conditions. This is being mentioned in the limitation. If author feel, this information is not helpful in Table 1, the same may be deleted.
4. Standard PB/MDT is mentioned in method section.