Global leprosy program: Does it need uniform-multi-drug therapy now?

World Health Organization (WHO) recently formulated its strategy for leprosy (period 2016–2020) in a draft document titled, "Universal Elimination of Leprosy, Towards Zero Disabilities Among New Child Cases Plan Period: 2016–2020."[1] This document proposes a broad-based action plan toward "Universal Elimination of Leprosy" with good strategic, operational changes for the elimination of leprosy.

However, this draft also states as one of its strategy to "promote use of shorter, uniform treatment regimen, uniform-multi-drug therapy (U-MDT)" for all categories of leprosy globally (through) in its executive summary. The document mentions that "prompt treatment with U-MDT regimen, which shortens the duration, will be the key tenets of the global leprosy strategy for the next 5 years (2016–2020)." In addition, it proposes as a part of intensified action to "improve case management including U-MDT" to reduce leprosy transmission.

In other words, WHO is planning to push for implementation of U-MDT globally as a key strategy for the years 2016–2020. Implementation of U-MDT would bring radical change in the duration of therapy for multibacillary (MB) leprosy as it reduces the duration of MDT MB regimen by half (6 months). Many leprosy workers in India are apprehensive and distraught about the long-term consequences of implementation of 6-month U-MDT for MB leprosy patients. Many strongly believe that its implementation in the present form can jeopardize the leprosy program that is already beleaguered due to various administrative reasons. The "Indian Association of Dermatologists Venereologists and Leprologists" (IADVL), which is one of the largest professional body of dermatologists and leprologists in the world comprising over 8000 members from all over India, is expressing similar apprehensions. Many members of the "Indian Association of Leprologists" are also concerned for this policy shift in the duration of treatment for MB cases.

It should be noted that the idea of shortening the duration of 12-month MDT MBR to make it a single U-MDT of 6 months for all types of leprosy was on the agenda of WHO from the time, it was first mooted by its Technical Advisory Group (TAG) in 2002.[2] Within a few months, it was endorsed, and research protocol approved by the TAG at its fourth meeting.[3] A multicentric study was planned to assess the effectiveness of 6-month MDT MBR for all types of leprosy patients through the general health services, in India and China. During the follow-up, patients are closely monitored for clinical response and for any complications. The long-term follow-up for assessing the effectiveness of the U-MDT study is the cumulative relapse rate at the end of 5 years after completion of the treatment.[4] WHO went ahead with its multicenter study with 8 centers in India and 2 in China. The study design originally aimed at recruiting 2500 paucibacillary (PB) and 2500 MB cases in each arm, but only 2094 PB and 1302 MB cases were recruited.[5] The detailed study design and its results are yet to be published.

CRITICISM OF PROPOSED UNIFORM-MULTI-DRUG THERAPY STUDY

Leprosy review in an editorial analyzing the scientific merits of the recommendation of a U-MDT regimen and its research protocol[6] considered it one of the most controversial recommendations, and that U-MDT is a premature attempt to shorten the duration of MDT for MB leprosy to 6 months. It also pointed flaws in the research protocol of U-MDT; that there is no "control group" of standard 12 months WHO MDT MB patients; 5 years relapse rates being based on finding one or more new skin patches which is too vague and that pooled relapse rates can mask an unacceptably high relapse rate among smear positive patients. It concluded that it is wishful thinking to ignore the fact that requirements of chemotherapy are different among various subgroups of leprosy patients and to recommend a uniform regimen for all leprosy patients.

RESULTS OF WORLD HEALTH ORGANIZATION MULTICENTER STUDY

The 12th meeting of WHO TAG on Leprosy Control[7] held in April 2014 reports that the preliminary results of the multicentric study on U-MDT are encouraging and might possibly lead to making leprosy treatment simpler. However, the interim report on U-MDT trial states vaguely that the efficacy of giving 6 months of MDT MB regimen to all types of leprosy was studied under program conditions. It mentions that the study had "relapse" as primary outcome measure and after 7 years of follow-up (expected 8 years), there were six relapses, four in MB and two in PB groups. This is surprising, as by the end 2008 itself the WHO TAG reported that there were six cases of relapses, four of them in MB cases.[5] There is no mention of bacteriological (skin smear) results as they were not a part of the study design. Although it is mentioned that final results are expected in 2016, it concludes by stating that U-MDT is acceptable for reduction of disease burden.

The outcome of U-MDT in bacteriological clearance, especially in patients with high bacteriological index, reactions, deformities, and clearance of skin lesions is crucial to study for considering any

proposal for its implementation. Moreover, the relapse cases are likely to be grossly underestimated without slit skin smear studies. The present proposed WHO recommendation appear to be founded on the results of studies reported in the 12th TAG meeting of 2014 based on its 2002 research protocol.[3] On careful scrutiny, it can be noted that all the objections raised in 2003 through the editorial of leprosy review[6] are very much valid even now.

DO WE NEED UNIFORM-MULTI-DRUG THERAPY AT THIS JUNCTURE AT ALL?

Rather than looking at the nitty-gritty of U-MDT multicentric study protocol and its results, it would be pertinent to ask ourselves a question as to whether "6-month U-MDT for all leprosy patients" is needed at all at this juncture for the global leprosy program. Let us analyze it.

UNIFORM-MULTI-DRUG THERAPY: FOR REDUCTION OF DISEASE BURDEN

The statement that U-MDT is acceptable for reduction of disease burden in the report of the 12th meeting of WHO TAG[5] indicates the principal purpose of promoting U-MDT by WHO, for the reduction of disease burden of leprosy world over. Now, we need to ponder over this as to whether such measures are required in the present day leprosy scenario. It is well-known that leprosy case numbers are falling in the world over during the last decade although new case detection rate appears to stagnate. The latest WHO global leprosy figures for 2014[8] reported as on the last day of first quarter of 2015 are as follows: The prevalence rate recorded was at 0.31 per 10,000 population, marginally less than that of 2014 (0.32 per 10,000 population). New cases reported from 121 countries were 213,899, which is at almost same level as in the previous year (215,656). In addition, the number of new cases globally over the past 10 years has shown a noticeable but slow decline from 299,036 in 2005 to 213,899 in 2014. In the year 2014, the new case detection rate at global level was 3.78 per 100,000 population. These numbers are neither threatening nor showing increase to warrant radical changes in the duration of therapy "to bring down the prevalence rate" of leprosy.

UNIFORM-MULTI-DRUG THERAPY: AS A OPTION TO TREAT MULTIBACILLARY LEPROSY EFFECTIVELY

It is accepted that the number and proportion of MB cases indicate the presence of advanced cases of leprosy and indirectly the magnitude of infection in the community. The leprosy figures for India for the year 2014 are as follows:[8] The registered prevalence was 88,833; new cases detected were 125,785 of which MB cases were 66,436 (53%). For the year 2014, the proportion of MB cases globally was 60.6%. These figures indicate that proportion of MB leprosy is more than PB leprosy world over including India and any intervention in the program should accommodate this trend. However, the proposed U-MDT serves well for PB leprosy but takes away precious 6 months of therapy for MB patients, without providing any additional interventions or support.

UNIFORM-MULTI-DRUG THERAPY: IS 6-MONTH MULTI-DRUG THERAPY MULTIBACILLARY REGIMEN SUFFICIENT TO TREAT MULTIBACILLARY PATIENTS WITH HIGH INITIAL BACTERIAL INDEX?

By the definition and classification of leprosy for therapeutic purposes, good percentage MB patients are always skin smear positive, a proportion of them with high initial bacterial index (BI). Such being the case, it is important that studies be first conducted to assess the effect of such shortened U-MDT on MB patients with high initial BI. Unfortunately, no such studies were conducted. In a U-MDT study from China,[9] out of 116 MB patients, 114 (68%) were smear positive indicating the high percentage of smear positives in MB groups. Importantly, the study reported that at the end of 42 months of follow-up post-U-MDT, 26.5% of patients were still smear positive. It is not understandable that why MB cases (including those with high BI) will be left half treated (with U-MDT) in the community?, will they not propagate secondary drug resistance, pose hidden reservoir of infection to others and who will follow-up such cases after release from treatment in the setting of integration of leprosy services into general health system in India?

UNIFORM-MULTI-DRUG THERAPY: IS IT EQUAL OR SUPERIOR TO 12-MONTH WORLD HEALTH ORGANIZATION MULTI-DRUG THERAPY MULTIBACILLARY?

The WHO open multicenter, noncomparative trial only considered "clinical response" and "cumulative relapse rate at 5 years" as basis for assessment. Neither slit skin smear nor histology was included as parameters for assessing the response. The U-MDT was found ineffective for MB leprosy when it was compared with 12 months WHO MDT-MB where clinical, bacteriological, and histopathological parameters were included. An open comparative study between WHO MDT and U-MDT regimen with follow-up of 24 months carried out in India[10] in 127 newly diagnosed untreated leprosy patients concluded that based on clinical, bacteriological, and histopathological parameters, U-MDT of 6 months duration was effective in PB leprosy but was too short a regimen to adequately treat MB leprosy patients. Other studies from Brazil too did not find U-MDT superior to 12 months WHO MDT-MB.[11,12]

NOW, BACK TO THE QUESTION, DOES THE LEPROSY PROGRAM NEED 6-MONTH UNIFORM-MULTI-DRUG THERAPY FOR ALL LEPROSY PATIENTS AT THIS JUNCTURE?

The current 12 months WHO MDT-MB regimen practiced globally is a robust and proven regimen to treat MB leprosy and has been effective in bringing down the leprosy burden substantially world over. Both health care providers and receivers are happy with the present 12-month WHO MDT-MB and as such there is no valid scientific reason or evidence to shorten duration of therapy for MB leprosy by 6 months. With the continued reduction in leprosy cases globally, the reason for shortening the duration cannot be budgetary constraints as well.

Based on the limited studies reported so far, the 6 months U-MDT is a good regimen for PB leprosy, but such shorter course was found inadequate for MB leprosy, and it is definitely not superior to presently used 12-month WHO MDT-MB regimen.[10-12] Many leprosy workers in India and elsewhere strongly feel that it should not be implemented in the present form until there is substantial evidence of its superiority over the present 12 months MDT MB regimen both in terms of clinical and bacteriological aspects, and not just in 5 years relapse rates. In conclusion, it can be stated that there is a paucity of evidence at present to support efficacy of 6-month U-MDT in all types of leprosy over current WHO MDT-regimens.

It is imperative that authorities working on this strategy document should have a re-look on long-term damage such a shortened U-MDT regimen can potentially have on the leprosy program in India and worldwide. Consequently, WHO should re-evaluate its strategy for the good of leprosy programs worldwide and put in abeyance the proposed implementation of U-MDT for MB leprosy in the present form in its proposed action plan for years 2016–2020, until it is studied and discussed thoroughly for evidence of its superiority over the present robust 12-month WHO-MB MDT regimen.

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