Editorial

UNIFORM MDT (U-MDT) REGIMEN FOR ALL LEPROSY PATIENTS—ANOTHER EXAMPLE OF WISHFUL THINKING

At the third meeting of the WHO Technical Advisory Group on Elimination of Leprosy (TAG), key challenges to ensuring integration and sustainability of leprosy services were identified as ‘to further simplify and shorten the current multidrug therapy (MDT) regimens’ and ‘to abolish classification for treatment purposes’.\(^1\) The most important and most controversial recommendations by the group were the ‘large scale implementation of accompanied MDT (AMDT)’ and the ‘implementation of the 6-month MB MDT regimen for all leprosy patients.’\(^1\) Later, the recommendation of a uniform MDT (U-MDT) regimen, based on the standard MDT regimen for MB leprosy:\(^2,3\) but with a duration of treatment of only 6 months for all types of leprosy, was endorsed, and a research protocol was approved by the TAG at its fourth meeting.\(^4\) Because an Editorial\(^5\) calling attention to the flaws of AMDT has recently been published in *Leprosy Review*, this paper focuses on scientific merits of the recommendation of a U-MDT regimen and its research protocol.

Progress from dapsone monotherapy for all types of leprosy to different MDT regimens for paucibacillary (PB) and multibacillary (MB) leprosy

The clinical, bacteriological, histopathological and immunological manifestations of leprosy form a continuous spectrum.\(^6\) Thus, classification has been an important subject in leprosy research and control. The host–parasite relationship differs greatly between the two poles of the leprosy spectrum, and their bacterial populations are different both quantitatively and qualitatively. A heavily infected lepromatous patient may harbour as many as \(10^{11}\) *Mycobacterium leprae*,\(^7\) and it has been observed that skin biopsy specimens from advanced lepromatous patients contained, on average, \(10^6\) *M. leprae* per mg of tissue.\(^8\) Such a large bacterial population probably includes spontaneously occurring drug resistant *M. leprae*.\(^9\) By contrast, a typical tuberculosis patient is skin smear negative; the size of the bacterial population is estimated to be no greater than \(10^6\),\(^2\) and is unlikely to include a spontaneously occurring drug resistant bacillus.\(^9\) Consequently, the requirements for chemotherapy, especially in terms of the number of drugs and the duration of treatment, differ between these groups. The observations that the disease tended to relapse in skin smear positive cases if dapsone monotherapy was discontinued,\(^10\) and that secondary dapsone resistance emerged almost exclusively in skin smear positive patients,\(^9\) illustrate the different requirements of smear-positive and smear-negative patients.
It is true that, during the era of dapsone monotherapy, all leprosy patients were treated with the same regimen. However, this does not mean that a uniform regimen was desirable; simply, that during that era, no other effective drug was available to supplement dapsone. When a WHO Study Group met in 1981 to discuss the chemotherapy of leprosy for control programmes, two major developments were taken into consideration. First, dapsone resistance, both secondary and primary, had become a widespread phenomenon, seriously jeopardizing the whole strategy and threatening the prospect of leprosy control. Second, a small number of bactericidal drugs became available for the treatment of leprosy, of which rifampicin was the most potent drug against *M. leprae*. Consequently, the most important recommendation made by the Study Group was to treat all leprosy patients with rifampicin-based MDT. In view of the different requirements of chemotherapy among leprosy patients, the Study Group classified leprosy into MB and PB cases according to the degree of skin smear positivity. This was essentially an operational classification to serve as a basis for chemotherapy, because the compositions and the durations of the MDT for MB and PB leprosy differed substantially.

**Over-treatment of PB leprosy by a U-MDT regimen**

Since the concept of PB leprosy was introduced, its definition has changed several times. Originally, PB leprosy included indeterminate (I), polar tuberculoid (TT) and borderline tuberculoid (BT) leprosy in the Ridley–Jopling classification, or patients with an initial bacteriological index (BI) of < 2 by the Ridley scale at all sites. Later, the WHO Expert Committee on Leprosy at its sixth meeting recommended that only patients who are initially skin smear negative should be classified as PB. Subsequently, at its seventh meeting, the WHO Expert Committee on Leprosy recommended that PB classification should be applied to those newly diagnosed patients who have no more than five skin lesions. The range of cases classified as PB leprosy has progressively narrowed over the last 20 years; only about 50% of newly detected leprosy patients are now classified as PB, significantly less than in the past. Employing the current definition, it is reasonable to suspect that PB patients may respond to chemotherapy more homogeneously, and probably with some self-healing.

Despite changes in the definition of PB leprosy, the composition and duration of the standard MDT regimen for PB leprosy remains unchanged. Several million PB patients have now completed their treatment; the great majority of them, classified by whichever definition, responded very well to the two-drug regimen administered for 6 months, and there is no major disagreement regarding the low PB relapse rate after MDT. One could therefore consider the possibility of shortening the duration of MDT for PB leprosy to less than 6 months. Although, in theory, monotherapy with rifampicin should be sufficient for the treatment of PB leprosy, in order to minimize the risk of emergence of rifampicin resistance among MB patients who have been wrongly classified as PB leprosy, it is safer to continue to use the two-drug combination.

However, the recommendation of a U-MDT regimen for all leprosy patients points to the opposite direction. Instead of shortening the duration of MDT for PB leprosy, the TAG has recommended treatment of PB leprosy with three drugs, daily dapsone and clofazimine plus monthly rifampicin and a supplementary larger dose of clofazimine, for 6 months. The recommendation to add clofazimine to the current MDT regimen for PB leprosy lacks any scientific indication or justification, and PB patients will be over-treated by the U-MDT
regimen. Furthermore, because clofazimine is a relatively expensive drug and may cause side-effects, implementing the U-MDT regimen would increase the cost of treating PB leprosy, and unethically expose patients to an additional risk of side-effects.

Premature attempt to shorten the duration of MDT for MB leprosy to 6 months

The flaws in recommending the U-MDT regimen for the treatment of MB leprosy are quite different; instead of over-treatment, MB patients might be under-treated by the U-MDT regimen. According to the TAG, the rationale for recommending a U-MDT regimen was that: ‘MDT has been shown to be robust in terms of treatment efficacy and safety. Relapse rates are very low (less than 1%), resistance to MDT is virtually non-existent, and relapse cases can still be cured by MDT.’ How true is this statement?

First, a regimen is defined both by its composition and its duration. Although the composition of the MDT regimen for MB leprosy has remained unchanged, the duration of treatment has been progressively shortened, from ‘at least two years and be continued, whenever possible, up to smear negativity’, to 24 months, and then to 12 months. With respect to efficacy, although there are data on long-term relapse rate after treatment with 24-month MDT, but there are none after 12-month MDT, which has been the regimen of choice for MB leprosy since 1998. Until this information becomes available, no conclusion can be reached regarding the long-term efficacy of 12-month MDT, and there can be no justification for further shortening the duration of MDT for MB leprosy to 6 months.

Secondly, there is disagreement on the magnitude of MB relapse after 24-month MDT and the possible existence of a higher-risk subgroup of MB patients who are more prone to relapse. TAG has completely ignored the observations of high relapse rates, as high as 4–7 per 100 patient years among patients with initial BI of ≥ 4.0, reported by some research institutes.

Thirdly, the conclusion that resistance to MDT is virtually non-existent or completely absent cannot be supported by evidence, because post-MDT surveillance for relapse was discontinued since 1994, and susceptibility to rifampicin has rarely been tested since the introduction of MDT. The history of leprosy has repeatedly demonstrated that a phenomenon may exist despite not being reported; the problems of poor-adherence to self-administered dapsone, and frequency of relapse caused by dapsone resistance were thought to be negligible, but became apparent only after serious studies were conducted. It would be more reasonable to conclude that, at present, the frequency of rifampicin resistant leprosy is unknown.

Flaws in the research protocol ‘Uniform MDT regimen for all leprosy patients’

According to the protocol, the project requires 5000 newly detected, previously untreated leprosy patients, 2500 MB and 2500 PB; patients will be examined clinically for evidence of relapse for 5 years after completion of treatment; and the maximum acceptable cumulative relapse rate has been predetermined at 5% at the end of 5 years.

The major flaws in the protocol are the following:

- There is no reason to include PB patients in a trial to determine relapse rate, because several million PB cases have already been successfully treated with 6-month standard MDT; thus half of the resources for the trial are being wasted.
• In the current protocol, there is no control group in which MB patients are treated with the standard 12- or 24-month MDT regimen. As a consequence, it will not be possible to compare the efficacy of the U-MDT regimen for MB leprosy with that of the standard MDT regimen.

• The definition of MB leprosy, i.e. all patients with more than five skin patches, is too broad, and will include many cases who are indeed PB leprosy from the bacteriological and chemotherapeutic points of view. As a research project, the tested subjects should be as homogeneous as possible, and therefore the study should focus only on skin smear positive patients.

• The definition of relapse, i.e. the finding of one or more new skin patches consistent with leprosy, is too vague; based on this definition, a health worker would have difficulty in distinguishing relapse from leprosy reaction. More important, because skin smear examination, one of the key indicators for diagnosing MB relapse, is not to be employed, the sensitivity and specificity of diagnosing MB relapse will be seriously compromised.

• The average incubation period of MB relapse after treatment with rifampicin-containing regimens is over 5 years. In order to detect the majority of MB relapses, patients should be followed for more than 5 years after stopping treatment, otherwise only a proportion of the relapses will be detected, leading to an over-estimation of the efficacy of the tested regimen.

• In routine programmes, the cumulative relapse rate for PB or MB leprosy is around 1% at 9 years after completion of standard MDT; there is no justification for accepting a predetermined cumulative relapse rate of 5% at the end of 5 years of the trial.

• The relapse rates for PB and MB cases—or more ideally, for smear-negative and smear-positive cases—should be calculated separately. A pooled relapse rate of all patients may mask an unacceptably high relapse rate amongst smear-positive individuals. For example, a 5% relapse rate would give 250 relapses in the study population of 5000; if there are only 200–400 cases with an initial BI of ≥ 4, a relapse rate of over 50% in this high initial BI subgroup would be needed before the U-MDT regimen was declared ineffective by the proposed criterion.

Conclusion

It is wishful thinking to ignore the fact that the requirements for chemotherapy are different among various subgroups of leprosy patients, and to recommend a uniform regimen for all leprosy patients. A U-MDT regimen would over-treat PB leprosy, waste substantial amounts of resources, and unethically expose patients to the risk of side-effects caused by clofazimine. Moreover, none of the reasons for treating MB leprosy with U-MDT regimen is valid. If one cannot exclude the possibility that MB patients, particularly those with a high initial BI, may be under-treated by U-MDT, there would be serious ethical problems in recommending the regimen. Substantial modifications are needed to address the flaws in the research protocol, otherwise it is likely that the trial will not reach a clear-cut conclusion; or even more seriously, that the study will produce an invalid conclusion in relation to the small subgroup of patients with high initial BI.

The website www.clinicalevidence.com contains a review of all the published literature on chemotherapy trials in leprosy.
References