

# The question of the "12 doses" of the multidrugtherapy for Hansen's disease

Editorial

The implementation of a new therapeutic regimen is accepted as the best practice in medicine after its efficacy and security have been adequately demonstrated in randomized, controlled and scientifically conducted essays. Such experiments would compare the efficacy and security of a new treatment or therapeutic regimen with the currently accepted treatment (Win H. Van Brake!).

That is why I become perplex in face of the OMS Technical Committee recommendation to shorten the treatment of multibacillary Hansen's disease patients to 12 months. Dr. Ji<sup>4</sup> Bahong in the editorial of the Leprosy Review in 1998 exposes arguments he considers favorable to this decision, but that are not accepted by other authors.

The microbiologist refer first to the definition of multibacillary (MB) patients, which has become wider since 1981 with the introduction of the MDT/WHO. In the beginning, the MB should have a bacilloscopic index (BI) equal or lower than 2; later on all cases of positive bacilloscopy would be considered MB; and then owing to the difficulties of having a reliable bacilloscopy done in the field, this practice was abolished and cases with more than 5 lesions have been considered as MB since then. That is why many cases that would have been diagnosed as paucibacillary (PB) started to be defined as MB and therefore, the number of these increased considerably. Thus, because half of these cases have negative bacilloscopy and the bacillary load of the positive cases is significantly lower than these cases were in the past, the period of treatment with the MDT could be reduced.

The statement that the number of bacilli from patients that have positive bacilloscopy is higher than in the past should be taken as an impression, because of the lack of data about it. On the other hand, this dilution of positive patients among the MB group should be more emphasized because those are the ones who maintain the endemy, and these are the cases in which relapses may occur if patients are not adequately treated. Waters says it is an irony that the fear of relapse in dimorphous leprosy patients has eventually led to a medical-political pressure to reduce the treatment of advanced lepromatous leprosy cases.

Secondly, it is said that the results of control programs and research projects have demonstrated that the rates of relapses after the MDT were very low, around 0,2% annually. It is still said that despite some reports have suggested that the rate of relapses after the MDT may be significantly higher among the MB patients with a high initial index (a mean BI>\_4,0), because they became relatively scarce in the field, they won't harm the control programs. If there are relapses among them, they should simply be retreated.

Making comments about those considerations, Patrick Linch, Director of the Nepal Leprosy Trust, refers to the fact that Dr. Ji<sup>4</sup> has been co-author of the study of the Institute Marchoux published in 1995, in a volume of the International Journal of Leprosy (IJL), in which he and the other authors conclude: "The relapses occur late (minimum 5±2 years) after the end of MDT". "The rate of relapses correlated with the bacillary load of the patient, it occurred more frequently among patients with a BI>\_4,0 before the MDT". "In order to avoid the frightening high rates of relapses, it is proposed that the duration of the MDT must be doubled to 4 years in patients with a mean BI>\_4,0 before the MDT". Dr Patrick thinks it is ironic that after two and a half years, one of the main authors of that study is now giving arguments for the shortening of the treatment to one fourth of the regimen proposed by themselves in 1995 (48 to 12 months). He says it is also ironic that in both articles, Dr. Ji<sup>4</sup> refers to the document WHO/CTD/LEP/94.1 that points out to a low rate of relapses after the MDT. In his most recent article he uses this information as the backbone to justify the 12 months of the MDT, while in the previous article we have been warned to interpret "carefully" the findings of the mentioned article. To say today that the indexes>\_4,0 are rare, when bacilloscopy is no longer done in the field, is rather precipitated. Dr. Patrick Lynch reports that the Nepal Leprosy Trust in its center in Lalgadh, in the District of Dhanusha, registered almost one fourth of all the new cases of Nepal registered during the fiscal year of 1997/98.

The proportion of MB to PB cases was 60% to 40%, and from the MB cases registered, almost 10% had a BI >\_4,0, this means 1 in each 10 MB patients being considered at "alarming high risk of relapse". Based on the

comments of Dr. Ji<sup>4</sup> related to the excessive diagnosis of leprosy, the real percentage would be higher. Dr. Win H. Van Brakel, also from Nepal, says that he doesn't think leprosy cases with high baciloscopic indexes are rare. He reports that bacilloscopy has been done in 80% of the MB cases at the time of diagnosis. From 2.346 diagnosed cases in recent years, and in which bacilloscopy was done, 308 (13%) had an initial index > 3+. This author also mentions the data from the Weekly Epidemiology Record (WER) of May 2nd, 1997. This publication shows that patients with high baciloscopic index are not rare. About 17% of the 142.844 new MB cases reported in 1995 had BI > 3. Dr. Brakel refers that in this publication there is a table showing that India registered an estimated number of 8.842 new cases with high baciloscopic index, and also Brazil with 5.388 cases, Indonesia 1.507, Nepal 1.374, Ethiopia 1.329 and Madagascar 980. Because of the poor conditions to perform bacilloscopy in the field programs of those countries, these data may be underestimated.

The third argument by Dr. Ji<sup>4</sup> refers to the fact that the main role of the Dapsone-Clofazimin (DDS-CLO) component of MDT is to assure the elimination of bacilli resistant to rifampicin, and the results of experimental procedures with the "nude mouse" as much as from a clinical trial, showed that this component had a better bactericidal effect than it was expected. Three months of daily treatment with the DDS-CLO component killed alone more than 99,999% of the viable mycobacteria, which suggests that all the mutant resistant to rifampicin can be eliminated by this association.

Since Shepard's first assay in the foot pad of the mouse, all Hansen's disease therapeutics has been based on the experimental data from this rodent species. Many drugs have been tested in this model as to its anti Hansen's disease activity, and have been discarded or not, in spite of the difficulties in extrapolating to human the results obtained. Even the bacterial resistance to sulphone, described under the clinical prospect since the first work by Floch from the French Guiana, its existence was only recognized when it could be demonstrated in the foot pad of mice. Most recently, the nude mouse has been used with the same purpose. The use of MDT is similarly being related to microbiological data where the knowledge about the tremendous bactericidal activity of rifampicin and its possible monthly use was crucial for its development. Despite all therapeutic recommendations by the WHO have been based solely on the data of one laboratory, which belongs to Dr. Ji<sup>4</sup> in Paris, it is a reliable organization that will also have to be in accordance with the information that administration of the DDS-CLO component of MDT for three months is equivalent to a single dose of rifampicin. It is interesting to consider that the results of inoculation in foot pad of

immunocompetent mice obtained so far, and in which the treatment of Hansen's disease is based, has demonstrated that both dapsone and clofazimin are essentially bacteriostatic and have a weak bactericidal activity.

Being aware of this new information about the activity of the DDS-CLO component, it is hard to understand why the MDT is not used only for 6 months. This is based on bacteriological data and would be useful for the operational and economic point of view because all patients, PB and MB, could be treated with a single therapeutic scheme for the same period of time.

The fourth argument of Dr. Ji<sup>4</sup>, related to the use of MDT for 12 months, is based essentially on a double blind multicentric study in which some countries take part, including Brazil. The study intends to compare four therapeutic regimens: a) rifampicin + ofloxacin for 1 month; b) MDT + ofloxacin; c) MDT for 1 year; d) MDT for 2 years.

He says that unpublished data allow him to state that 12 months of MDT is as effective as 24 months with the same regimen. Despite the codes have not been officially opened, Dr. Ji<sup>4</sup> must have had access to some results, however, I think it is unlikely that the initial baciloscopic indexes of each experimental group have already been tabulated and the number of patients with baciloscopic index higher than 2 counted (the minimum required index to be admitted to one of these groups). Besides, as Dr. Walters observes, a 7 to 10 years of follow up is desirable in order to verify the rate of relapse, and some more time is needed to attain the goals of this multicentric study.

The fifth and last point presented by Dr. Ji<sup>4</sup> refers to patients recovered after having abandoned the MDT after several periods of treatment. He comments two studies in which recovered patients were negative in the bacilloscopy and only a small portion remained positive. He thinks the data obtained suggests a satisfactory effect of the 12 month treatment with the MDT, nevertheless he acknowledges that we must be careful to interpret the information obtained from retrospective analysis because the files are frequently incomplete, the sample size is relatively small and the pre-treatment characteristics of patients between the groups may not be comparable.

It is our understanding that the care in evaluating these results is linked to the initial baciloscopic index of patients who abandoned the treatment and recovered after variable periods of time, which are not mentioned. In spite of raising discussion, it is clear that the only criterion for cure is the negative bacteriological result of the patients, and this is strictly related with the initial bacillary load. That is why based on the results obtained from patients who recovered, it is impossible to

recommend a single 12 months regimen for MB patients.

In the last International Leprosy Congress, in Beijing in 1998, the workshop on therapeutics was not clear if the data was sufficient to recommend a formal "12 doses" treatment, however, in the plenary session it was admitted that the use or not of this regimen would be responsibility of the professional or the country involved in the control programs.

Since 1997, the information about the "12 doses" in the specialized literature is found only on editorials, letters to editors, conclusions of the WHO Technical Committee, and from the Congress of China, in results of the workshop on therapeutics, and the presentation of three papers, one by Grosset and Ji Bahong, another by Ganapati et al. reporting observations about 50 patients, and the last one by Amar Kant Jha Amar, who studied 3.740 MB patients in 1 and 2 years regimens with a 5 years follow - up. This isn't enough.

Van Brakel says that today once the bacilloscopy is not done in the field, it is not possible to treat patients with higher or lower bacilloscopic index in different regimens, therefore all the MB patients would receive the same treatment independent of the initial bacilloscopic exam.

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We agree with this author who considers unethical to use the 12 months treatment for patients with high bacilloscopic index, as much as it would be unethical to treat any MB patient with this regimen once it is no longer possible to determine their bacteriological status.

Dr. Ji, however, concluding his editorial about the "12 doses" of MDT says the recommendation was accepted by almost all the leprosy control programs of the main endemic countries and it has been implemented.

There is no way to change a politically defined situation. The only thing we can do is to hope everything turns out all right and the patients do not suffer with the chosen measures. Anyway, any positive result will be more a result from the Holy Spirit than a consequence of decisions taken in an ethical and scientific manner.

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