Treatment of leprosy reactions

Editorial

This editorial is a response to Dr Pannikar's statement that "there is no place for thalidomide in the treatment of ENL" in the World Health Organization (WHO) Pharmaceutical Newsletter of February of this year.

Thalidomide was given some credit again after Sheskin (1965; 1970; Sheskin *et al.*, 1969) proved the affectivity of this drug in the treatment of erythema nodosum leprosum (ENL). After its teratogenic action came into evidence, the therapeutic activity of thalidomide in leprosy type II reactions was demonstrated, as well as its effectiveness in other serious conditions such as chronic and discoid erythematodes lupus, Behçet syndrome, Hyde's nodular prurigo, actinic prurigo, aphta. It also showed to be effective in some manifestations of AIDS, in neoplasias (e.g. multiple myeloma), and some other conditions. It became clear that thalidomide is a drug of extraordinary value (PENNA *et al.,* 1998). It also had shown that care must be taken with interpretations of drug trials before releasing a drug to be marketed.

There were reasons for astonishment of the editor, that followed the release of a paper (PANNIKAR, 2003) in which a WHO representative states that the activity of thalidomide in minimizing the symptoms of ENL is mainly due to its anti-pyretic activity, and adds that studies have shown that clofazimine is the drug of choice for the control of relapsing chronic ENL reactions, since it exhibits anti-leprosy and anti-reaction effects.

Concerning thalidomide, its anti-pyretic action is well known during the first 24 hours after administration to a ENL patient, but what happens thereafter is even more important, the reactional episode resolves within 3 to 4 days. The effect on neural lesions is not that clearly noted, and that is why in acute neuritis corticosteroids are favored.

There have been several studies showing the efficacy of thalidomide in type II leprosy reactions (OPROMOLLA *et al.*, 1966; PENNA *et al.*, 1998; RAMANUJAM *et al.*, 1975; SHESKIN, 1965; SHESKIN *et al.*, 1969; SHESKIN, 1970) and the WHO itself has initiated a multicenter trial proving the therapeutic activity of this drug (IYER *et al.*, 1971).

The conclusion that clofazimine is superior to thalidomide in the WHO Pharmaceutical Newsletter is based on 7 papers mentioned. In the first, Browne (1965) refers to 13 lepromatous patients treated with clofazimine (B663) only, 7 for 6 months and 5 for 12 months. He himself concludes that the number of patients was too small, the treatment too short and there were no adequate controls to prove that the drug has an anti-inflammatory effect resulting in less ENL type reactions. The second article is a symposium abstract from the 9th International Congress held in London in 1968 (WATERS, 1968). This meeting about "B663 (Lampren, Geigy) in Leprosy and Leprosy Reactions Treatment" was organized by J.R. Geigy S.A. and Geigy (UK) Ltda., and had Dr. M.F.R. Waters as "chairman". No formal work was presented and a lower ENL incidence with the use of the B663 was claimed based on the investigations of 11 researchers who used a variety of methods, including internally controlled, paired and non-controlled studies. However, there are no recorded bibliographic references of these studies. Another work was a double blind study coordinated by the WHO in which superior activity of thalidomide compared to acetylsalicylic acid was demonstrated in the treatment of ENL, because of the anti-pyretic activity and reduction of the skin lesions. There was no reference to clofazimine in this paper (IYER *et al.*, 1971). The fourth and fifth papers referred to were almost identical articles published in different journals. The first one with 61 patients was published in 1975 (RAMANUJAM *et al.*, 1975) and the second with 72 patients was published in 1976 (IYER *et al.*, 1976). An interesting conclusion of the first article was: *"because clofazimine takes 8 to 12 weeks to demonstrate an anti-inflammatory effect, in severe reactional cases or when painful manifestations are predominant, the use of corticosteroid, in addition to clofazimine, is mandatory for quicker results"*. In the second, there is also a worth mentioning citation: *"thalidomide was chosen as a control drug because in a previous study it showed to have a remarkable effect in reactional episodes of patients dependent on corticosteroids"*. In his discourse about clofazimine, the other two papers mentioned by the WHO representative are related to the presence of this drug in the multidrugtherapy (MDT) and its role reducing the frequency and severity of ENL episodes around the world. In the first paper, Becx Bleuminck *et al.* (1992) refer that there are few reports about the number of reactional episodes during therapy and in the patients studied by them, only 9,9% of 405 reactional episodes were ENL. These authors state that the anti-inflammatory effect of daily clofazimine 50 mg seems adequate to prevent ENL type reactions in many patients. It is necessary to emphasize that severe ENL episodes were the reason to refer the patients to the hospital implicating that if mild ENL were included, there would have been more

episodes. In the second paper, Willcox (1997) states that the ENL incidence decreased after MDT has taken over monotherapy and cites a personal communication with Diana Lockwood saying that reactions have been occurring in 20% and 10% of "BL" and "LL" patients respectively. The author highlights to be a pity that the only experiment comparing monotherapy with MDT has not used the WHO/MDT scheme. The author also emphasizes the anti-inflammatory and bactericidal activity of clofazimine and refers to the work by Birte *et al*. showing complete remission of neuritis symptoms, except for anesthesia, in 15 out of 20 ENL patients treated with this drug, and reduced severity of reaction in the other 5 patients. Finally, citing another personal communication with Diana Lockwood in which she believes clofazimine is the responsible for the decreased risk of ENL observed after the WHO/MDT was instituted, the author states that unfortunately no studies of enough quality has been conducted to prove this.

Therefore, the studies on which the WHO representative based his conclusion that clofazimine is the drug of choice for the treatment of ENL, instead of thalidomide, have proven nothing. They indeed indicate a slightly convincing anti-inflammatory activity of clofazimine. If this activity is real, it must however be low. Its effect on type II leprosy reactions is based mostly on personal opinions and not on well conducted studies, and the statement that daily clofazimine 50 mg in the MDT is the responsible for decreased ENL incidence is not consistent, at least considering the data shown so far.

It is worth to remember the conclusions drawn by the Therapeutic Commission at the International Congress held in Bergen (1973), stating that daily clofazimine 200 to 300 mg might be used in ENL episodes, nevertheless, if the anti-reactional effect was not observed in 6 weeks, it should be associated either with thalidomide or corticosteroids. This conclusion, based on the opinion of recognized experts, shows first that thalidomide is efficacious, and second, that when clofazimine effect is observed, it has a slow and inconstant action, being necessary to associate it with other drugs if the effect is not observed within one and a half months. It may be pointed out that in order to show anti-reactional activity, doses above 100 mg daily are necessary, and it should not be forgotten that this conclusion was drawn at a time when sulphone monotherapy was used and in some researcher's opinions, ENL episodes were more frequent.

How could the "behavior" of clofazimine change so much, decreasing ENL incidence at a daily dose of 50 mg in the WHO/MDT scheme, and acting in conjunction with rifampicin, a drug supposed to increase the incidence of type II reactions?

This work at the "WHO-Pharmaceuticals Newsletter" is worrisome. It tries to diminish the image of a medication greatly active in leprosy type II reactions and gives emphasis to the doubtful activity of another drug on these acute phenomena, a drug, clofazimine, that still needs to undergo well designed experimental studies to prove its action.

Similar behavior has guided the recommendations of the duration of the therapeutic antibacterial schemes which have changed to 12 months and 6 months, for multibacillary and paucibacillary patients respectively, without enough studies to prove the efficacy of such schemes.

In my opinion, such attitudes constitute in abuse of power.

Diltor V. A. Opromolla

REFERENCES

1. BECX-BLUEMINK, M.; BERHE, D. Occurrence of reactions, their diagnosis and management in leprosy patients treated with multidrug therapy; experience in the Leprosy Control Programme of All Africa Leprosy and Rehabilitation Training Centre (ALERT) in Ethiopia. *International Journal of Leprosy*, v. 60, n.2, p.173-184, 1992.

2. BROWNE, S. G. B663 – possible anti-inflammatory action in lepromatous leprosy. *Leprosy Review*, v.36, p.9-11, 1965.

3. CONVIT, J.; SOTO, J. M.; SHESKIN, J. Thalidomide therapy in the lepra reaction. *Int. J. Leprosy*, v.35, p.446-451, 1967.

4. 10th CONGRESO INTERNACIONAL DE LA LEPRA. Therapeutic Commission. Bergen-Noruega, 13-18 de agosto, *Anais*, 1973.

5. IYER, C. G. et al. WHO coordinated short term double blind trial with thalidomide on the treatment on the treatment of acute lepra reactions in male lepromatous cases. *Bull World Health Org*., v.45, p.719-732, 1971.

6. IYER, C. G.; RAMU, G. An open trial with clofazimine in the management of recurrent lepra reaction using thalidomide as a control drug. *Leprosy in India*, v. 48, p.690-702, 1976.

7. OPROMOLLA, D.V.A.; LIMA, L.S; MARQUES, M.B. Thalidomide in acute symptoms in leprosy (erythema nodosum or multiforme). *Hospita*l, Rio de Janeiro, v.69, n.4, p.827-44, 1966.

8. PANNIKAR, V. The Return of thalidomide: new uses and renewed concerns. *WHO Pharmaceutical Newsletter*, n. 2, february, 2003. p.11-12.

9. PENNA, G. O.; PINHEIRO, A. M. C.; HAJJAR, L. A. Talidomida: mecanismo de ação, efeitos colaterais e uso terapêutico. *An. bras. Dermatol.*, v.73, n.6, p.501-514, 1998.

10. RAMANUJAM, K.; IYER, C.G.; RAMU, G. Open trial with clofazimine in the management of recurrent lepra reaction anf of sulphone sensitive cases: a preliminary report. *Leprosy Review*, v. 46(supplement), p.117-120, 1975.

11. SHESKIN, J. Further observation with thalidomide in lepra reactions. *Leprosy Rev*., v.36, n.4, p.183-7, 1965.

12. SHESKIN, J.; CONVIT, J. Results of a double blind study of the influence of thalidomide on the lepra reaction. *Int. J. Leprosy*, v.37, n.2, p.135-46, 1969.

13. SHESKIN, J. Recent experience with thalidomide in Hansen's disease. *Int. J. Dermatol*., v.9, n.1, p.56-8, 1970.

14. WATERS, M. F. R. Transactions of the Ninth International Leprosy Congress. *International Journal of Leprosy*, v.36, p.560-561, 1968.

15. WILLCOX, M. L. The impact of multidrug therapy on leprosy disabilities. *Leprosy Review*, v. 68, p.350-366, 1997.