Acute Renal Failure and Multidrug Therapy for Leprosy

TO THE EDITOR:

Brasil, *et al.* ([2]) reported that a surveillance system for adverse drug reactions detected 20 cases of acute renal failure (ARF) among 20,667 patients treated for leprosy with World Health Organization multidrug therapy (WHO/MDT) in the state of São Paulo, Brazil, during an 18-month period. Assuming that the incidence of ARF in the general population in Brazil is around 140 per million, the same as that observed in Britain ([3]), these events follow a Poisson distribution, and one can calculate that the probability of the finding of 20 or more cases being due to chance is almost nil [calculations not shown, formula provided in Bégaud, *et al.* ([1])]. Brasil, *et al.* did not report whether the diagnosis of ARF was validated or simply accepted according to what was written on the notification. But even if only 7 cases out of the 20 were valid, the probability of a value as or more extreme than 7 (i.e., the p value) would still be less than 5%, which can be interpreted as an association between ARF and MDT for leprosy is likely.

The finding of an incidence of 1 per 1000 of ARF among patients under treatment for leprosy in São Paulo deserves, therefore, attention. Although not a common side effect, it is a severe one, and can lead to death if not adequately treated. It can be argued though that the available data are too crude and subject to biases. By this reasoning, one should not accept the data, which could eventually result in interference with the MDT program and may compromise the effort to control leprosy, because the cases of reported ARF are clearly associated to the drugs, and that an excess risk of developing ARF among users of WHO/MDT, supposedly due to the intermittent use of rifampin, is better demonstrated.

There should then be a next step in the investigation of the association between ARF and MDT. A detailed study of the reported cases would be of extreme interest in order to assess whether renal failure did occur and, if so, whether it was really acute and not previously unrecognized chronic renal failure. For each case, if the diagnosis of ARF was correct, then it would be necessary to assess whether WHO/MDT was correctly imputed as causally related to this complication. Other factors, such as other drugs, toxins, infections, dehydration, and so on, could be present simultaneously, and the likelihood of each should be compared, which could be done using one of several algorithms available in the literature [e.g., in Kramer, *et al.* ([5])] or, alternatively, by a Bayesian approach ([4]), or by both. Validation of case reports is essential for establishing whether there is an excess risk of ARF associated with WHO/MDT and, if so, what is its magnitude.

If this excess risk is confirmed, it would be interesting to investigate whether there are predictors of ARF among patients being treated with WHO/MDT, such as age, underlying diseases, or simultaneous exposure

to other drugs, the knowledge of which would help to eventually identify groups at risk. This could be achieved by the undertaking of a case-control study in a population of individuals with leprosy in which the cases would be those who had ARF, and the controls a sample of those who did not. It is important to use incident cases and appropriate controls in such studies, but even cases which already occurred, such as those detected by the São Paulo state surveillance system, could be used insofar as the selection of controls is adequate ([6]). The identification of risk groups could be extremely helpful for health professionals, who could use this information to identify individuals who should either be monitored as to their renal function during WHO/MDT or should receive an alternative drug schedule to treat their leprosy with a lower risk of developing ARF as a drug reaction.

—Sergio de A. Nishioka, M.D., M.Sc.

Centro de Ciencias Biomedicas
Universidade Federal de Uberlandia
Av. Para 1720
38400-902 Uberlandia, MG, Brazil

REFERENCES

1. Bégaud, B., Moride, Y. and Haramburu, F. Quality improvement and statistical calculations made on spontaneous reports. Drug Info. J. **28** (1994) 1187–1195.
2. Brasil, M. T. L. R. F., Opromolla, V. A., Marzliak, M. L. C. and Nogueira, W. Results of a surveillance system for adverse effects in leprosy's WHO/MDT. Int. J. Lepr. **64** (1996) 97–104.
3. Feest, T. G., Round, A. and Hamad, S. Incidence of severe acute renal failure in adults: results of a community based study. Br. Med. J. **306** (1996) 97–104.
4. Kramer, M. S. A Bayesian approach to assessment of adverse drug reactions: evaluation of a case of fatal anaphylaxis. Drug Info. J. **20** (1986) 505–517.
5. Kramer, M. S., Leventhal, J. M., Hutchinson, T. A. and Feinstein, A. R. An algorithm for the operational assessment of adverse drug reactions: I. Background, description, and instructions for use. JAMA **242** (1979) 623–632.
6. Wacholder, S., McLaughlin, J. K., Silverman, D. T. and Mandel, J. S. Selection of controls in case-control studies. I. Principles. Am. J. Epidemiol. **135** (1992) 1019–1028.