Intermittent treatment for TB and resistance

Tratamento intermitente para TB e resistência

Marcus Barreto Conde

Studies published in the 1950s and 1960s showed no differences between TB inpatients and TB outpatients regarding cure rates, recurrence rates and incidence of TB in people who have been in contact with these patients; such studies were the scientific substrate for the adoption of outpatient care for TB.[1-3] However, the adoption of this treatment regimen in daily practice rapidly revealed adherence problems, which were not so evident in the research environment. In this scenario, studies have been carried out to investigate the utility of intermittent treatment regimens as a facilitation tool to supervise TB treatment.[4,5] In the current issue of the Brazilian Journal of Pulmonology, Alvarez et al.[6] present the prevalence of resistance to *Mycobacterium tuberculosis* in the city of Brasília, Brazil, in cases in which the therapeutic regimen was rifampin-isoniazid-pyrazinamide combination for two months, followed by rifampin-isoniazid combination for four months (2RHZ/4RH), intermittently (three times a week) and self-administered during the continued treatment.[6] The question of the study was whether the self-administered intermittent regimen was associated with a higher rate of resistance to *M. tuberculosis*. The data used by the authors are from the national survey carried out between 1995 and 1997; the study showed that the rates of primary resistance and acquired resistance to isoniazid in Brasília were 4.6% and 15.8%, respectively.[6]

The most common causes for resistant bacilli selection are the resistance to one or more anti-TB drugs since the beginning of the treatment (primary resistance) or nonadherence to treatment. Among the various levels of nonadherence, the most frequently associated with resistance are treatment abandonment, poor compliance (to take and to stop taking the drugs at irregular periods of time) and inappropriate use of medication (to take only some of the drugs prescribed). Regardless of the mechanism, the final result is the same: therapeutic failure or disease recurrence. The history of previous treatment establishes, with a reasonable level of safety, the relationship between the first TB episode and the occurrence of acquired resistance at the second TB episode.[7] However, a review of nine international clinical trials involving the three drugs used in Brazil (rifampin, isoniazid and pyrazinamide) showed that only 6% of the cases of TB recurrence (11 of 178 cases) were resistant to isoniazid.[7] Such findings suggest that among the cases of TB initially sensitive to the drugs, up to 94% of the recurrence cases would also be sensitive. In the study of Alvarez et al.[6], the rates of acquired resistance to isoniazid were far greater than 6%, both in Brasília (15.8%) and in Brazil (21.9%). The fact that the treatment in the clinical trials was totally supervised (two of which were intermittent regimens) suggests that acquired resistance in the population investigated by Alvarez et al.[6] was related to adherence problems. The rates of primary resistance to isoniazid (4.6% in Brasília and 6.8% in Brazil) and the high rates of treatment abandonment reported in that study (approximately 25% both in Brasília and in Brazil) corroborate this hypothesis. In addition, the risk of therapeutic failure in cases of primary resistance to isoniazid or to rifampin among patients receiving a regular RHZ regimen is low.[7] Therefore, it would be interesting to know the number of retreatment cases due to treatment abandonment, disease recurrence, treatment failure, poor compliance and inappropriate use of medication. A retrospective study carried out in Brazil did not show significant differences in resistance rates between retreatment cases due to treatment abandonment and those due to disease recurrence; it showed, however, a resistance rate significantly higher in cases of treatment failure.[8] Nevertheless, a clinical trial carried out in Rio de Janeiro, Brazil, in which the control arm received the RHZ+ethambutol (RHZE) regimen five times a week in the first eight weeks and an intermittent regimen (with adjusted dosage) twice a week in the continuation phase, under direct observation, reported only four cases of recur-

rence after cure; all such cases were sensitive to isoniazid and rifampin, which corroborates the hypothesis that recurrence of an initially sensitive case is also sensitive.[9]

The principal conclusion of Alvarez et al.[6] was that there was no significant difference between the rates of resistance of patients receiving intermittent treatment regimen and those of patients receiving daily treatment regimen. This finding was expected, since it has been shown that the cycle of bacilli growth following a drug-free period, cycle which could be responsible for the development of resistant strains in individuals under intermittent treatment regimen, is only observed when the intermittence occurs weekly (once a week) and not when the drug is taken two or more times a week (with adjusted dosage).[5]

Although the data presented by Alvarez et al. reflect the reality of almost two decades ago, recent data from a study of national prevalence (unpublished) and information from the Brazilian National Tuberculosis Control Program (personal communication) show that the rate of resistance to isoniazid has increased. Therefore, a fourth drug, ethambutol, will be added to the treatment regimen, and the 2RHZE/4RH regimen will be administered as a fixed-dose combination, i.e., the four drugs in one single tablet. The four-drug regimen has been used practically worldwide because of the increasing rate of resistance to isoniazid, and this initiative of the Brazilian National Tuberculosis Control Program is welcome. However, some points merit reflection. It is known that among the TB cases with initial resistance to isoniazid only or to rifampin only the chances of treatment failure with the RHZ regimen exist, however small, and that the use of the RHZE regimen reduces these chances to practically zero. However, the chances of treatment failure in cases presenting other patterns of drug resistance (e.g., resistance to rifampin+isoniazid or to isoniazid+ethambutol) and treated with the RHZ regimen is high and remains high even with the use of the RHZE regimen.[7] In addition, since the addition of a fourth drug to the combination tablet increases the risk of problems to the bioavailability of rifampin, great care must be devoted to the quality standard of the fixed-dose combination tablet. In this context, it is of great importance that the results of these interventions be monitored, as occurs in phase IV clinical trials, and that medical centers capable of collecting data in compliance with the Guidelines for Good Clinical Practice provide information that allows us to evaluate the impact of such interventions.

The study of the article of Alvarez et al.[6] also brings up a curiosity. Although there are data suggesting that self-administered daily regimens and self-administered intermittent regimens are not different, further information regarding the results of the latter in an operational setting is needed.[10]

The increasing rates of resistance, as well as the possible low adherence associated with these rates, suggest that in addition to the use of a fourth drug and a fixed-dose combination tablet (measures intended to fight primary resistance to isoniazid and inappropriate use of medication), it is necessary to search for tools that will reduce the number of poor compliance cases and the rates of treatment abandonment. Furthermore, we should spare no efforts to perform cultures and sensitivity tests for all TB patients.

Marcus Barreto Conde
Adjunct Director of Research in the Thoracic Diseases Institute of the Federal University of Rio de Janeiro, Rio de Janeiro, Brazil

References

1. Tuberculosis Chemotherapy Centre Madras. A concurrent comparison of home and sanatorium treatment of pulmonary tuberculosis in South India. Bull World Health Organ. 1959;21:51-144.
2. Dawson JJ, Devadatta S, Fox W, Radhakrishna S, Ramakrishnan CV, Somasundaram PR, et al. A 5-year study of patients with pulmonary tuberculosis in a concurrent comparison of home and sanatorium treatment for one year with isoniazid plus PAS. Bull World Health Organ. 1966;34(4):533-551.
3. Kamat SR, Dawson JJ, Devadatta S, Fox W, Janardhanam B, Radhakrishna S, et al. A controlled study of the influence of segregation of tuberculous patients for one year on the attack rate of tuberculosis in a 5-year period in close family contacts in South India. Bull World Health Organ. 1966;34(4):517-532.
4. Mitchison DA, Dickinson JM. Laboratory aspects of intermittent drug therapy. Postgrad Med J. 1971;47(553):737-41.
5. A controlled comparison of a twice-weekly and three once-weekly regimens in the initial treatment of pulmonary tuberculosis. Bull World Health Organ. 1970;43(1):143-206.

6. Alvarez TA, Rodrigues MP, Viegas CA. Prevalence of drug-resistant *Mycobacterium tuberculosis* in patients under intermittent or daily treatment. J Bras Pneumol. 2009;35(6):555-560.
7. Mitchison D A. How drug resistance emerges as a result of poor compliance during short-course chemotherapy for tuberculosis. Int J Tuberc Lung Dis 1998; 2: 10-15.
8. Melo FA, Penteado CB, Almeida EA, Spada DT, Santos MA. Resistência pós-primária do *Mycobacterium tuberculosis* às drogas antituberculosas segundo os antecedentes terapêuticos em uma unidade de referência na cidade de São Paulo. Bol Pneumol Sanit. 2002;10(2):21-26.
9. Conde MB, Efron A, Loredo C, De Souza GR, Graça NP, Cezar MC, et al. Moxifloxacin in the Initial Therapy of Tuberculosis: A Randomized, Phase 2 Trial. Lancet. 2009;373(9670):1183-9.
10. Castelo A, Jardim JR, Goihman S, Kalckman AS, Dalboni MA, da Silva EA, et al. Comparison of daily and twice-weekly regimens to treat pulmonary tuberculosis. Lancet. 1989;2(8673):1173-6.