It Is Too Early to Discount the Contribution of Isoniazid to the Treatment of Tuberculous Meningitis

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(See the article by Thwaites et al., on pages 79–88.)

Standard treatment of tuberculosis in the United States includes multiple drugs, to prevent relapse and the development of drug resistance. Both pulmonary and extrapulmonary disease are treated with a 4-drug regimen—isoniazid, rifampin, pyrazinamide, and ethambutol—during the 2-month initiation stage, followed by 4 months of isoniazid and rifampin. Treatment outcomes in studies of isoniazid-resistant pulmonary tuberculosis are similar to those in studies of drug-susceptible disease [1, 2]. These studies included isoniazid and rifampin throughout, usually in addition to other drugs. The number of drugs in the regimen correlated with better outcomes, as did inclusion of pyrazinamide throughout. However, no controlled studies have been conducted of the treatment of isoniazid-resistant disease with a regimen that does not include isoniazid. Many experts believe that isoniazid contributes to treatment when resistance is of a low level [3]. The Tuberculosis Trials Consortium/US Public Health Service is currently evaluating outcomes in isoniazid-intolerant patients and in isoniazid-resistant pulmonary disease; in the study, patients are randomized to receive a regimen of rifampin, ethambutol, and pyrazinamide daily or thrice weekly for 6 months.

In this issue of The Journal of Infectious Diseases, Thwaites et al. [4] report comparable outcomes in a prospective study of 180 adults (defined as those >14 years old) with either drug-resistant or drug-susceptible tuberculous meningitis (TBM). Patients received 3 months of daily oral isoniazid (5 mg/kg), oral rifampin (10 mg/kg), oral pyrazinamide (25 mg/kg), and intramuscular streptomycin (20 mg/kg), followed by 6 months of oral isoniazid, rifampin, and pyrazinamide. Ethambutol was substituted for streptomycin for HIV-infected patients and was added to the initial 3 months of treatment for those treated previously for tuberculosis. All patients with multidrug-resistant (MDR) TBM died. In contrast, after 9 months of treatment, the patients infected with organisms resistant to isoniazid (with or without resistance to streptomycin) had outcomes that were similar to those in the patients infected with fully sensitive organisms. Times to fever and coma clearance were not significantly different, but the rate of bacterial clearance from the cerebral spinal fluid (CSF) was significantly slower in the patients infected with drug-resistant organisms. Thwaites et al. conclude that the study “failed to show a significant association between isoniazid resistance (with or without streptomycin resistance) and any clinical outcome measure, despite showing that drug-resistant organisms take significantly longer to clear from the CSF” (p. 86). Although they noted that it was possible that “the intracerebral concentrations of isoniazid exceeded the MIC of drug-resistant organisms” (p. 86), they suggested that “the most plausible explanation for the observed lack of effect of isoniazid resistance on outcome is that the relative roles played by isoniazid, rifampin, and pyrazinamide are similar in the treatment of TBM and pulmonary tuberculosis” (p. 87). They cited as support for this explanation the uniformly poor outcome in their patients with MDR TBM and the lack of convincing data from numerous studies of the treatment of pulmonary tuberculosis.

Thwaites et al. identified isoniazid resistance by the proportion method, using a single drug concentration for isoniazid (0.2 mg/L). Isolates were identified as being resistant if the number of colonies growing on drug-containing medium was ≥1% of that growing on drug-free medium. Isolates were not tested at an isoniazid concentration of 1.0 μg/mL, as is recommended by the National Committee for Clinical Laboratory Standards [5] and treatment guidelines for tuberculosis endorsed by the American Thoracic Society, the Centers for Disease Control and Prevention, and the Infectious Diseases So-
the crucial role attributed to isoniazid is based on its excellent penetration into the CSF and the limited penetration of rifampin. Ellard et al. [6] reported mean isoniazid CSF concentrations of 1.9 mg/L at 2 h and 3.2 mg/L at 4 h after oral doses of ~9 mg/kg had been administered. After administration of oral doses of ~11 mg/kg, penetration of rifampin into the CSF resulted in a peak CSF concentration of 0.78 mg/L, only slightly higher than its MIC of 0.3 mg/L. These experiments were done early during the course of disease, when better penetration of rifampin might be expected because of the impairment of the blood-brain barrier. In clinical trials of drugs for the treatment of tuberculosis, it has not been shown that the MIC and peak drug concentration are associated with treatment outcomes. Experience with other microorganisms might suggest that the projected peak CSF concentration of isoniazid (at least 10 times the MIC, which is generally accepted to be ~0.2 μg/mL) could provide therapeutic benefit in the treatment of TBM, but the effectiveness of rifampin, which has a MIC much closer to the peak CSF concentration achieved, is questionable.

As part of a Tuberculosis Trials Consortium/US Public Health Service randomized trial comparing once-weekly isoniazid and rifapentine with standard twice-weekly isoniazid and rifampin, Weiner et al. [7] reported that isoniazid plasma concentrations and rapid acetylator status were associated with failure and relapse in patients receiving once-weekly isoniazid and rifapentine for pulmonary disease. The association was noted only in the once-weekly rifapentine arm of the study but nonetheless sheds light on the importance of isoniazid as a companion drug, even in the continuation stage of therapy. Early clinical studies suggested that isoniazid provided therapeutic benefit against isolates with low levels of resistance, especially when administered in higher doses [8]. Murine studies also provide support for the activity of isoniazid in this setting [9]. Improved survival from infection with the strain W variety of MDR Mycobacterium tuberculosis, which is susceptible to higher concentrations of isoniazid, was noted when isoniazid was included in the treatment regimen [10]. In a US Public Health Service trial, doses of rifampin <600 mg were correlated with an increased risk of failure and relapse [11].

In the study by Thwaites et al., the small sizes of the patient groups and the relatively poor outcome in the group of patients infected with fully sensitive organisms may have led to bias against a negative impact of isoniazid resistance. The patients were grouped on the basis of whether their infecting organisms were fully sensitive, resistant to isoniazid only, resistant to streptomycin only, resistant to both isoniazid and streptomycin, or MDR. The patients infected with fully sensitive organisms experienced 28.7% mortality, and 44.4% fully recovered. The patients infected with organisms resistant to streptomycin only experienced 16.7% mortality, and 54.1% fully recovered. The patients infected with organisms resistant to isoniazid (whether or not they were also resistant to streptomycin) experienced 37.8% (14/37) mortality, and 27.0% fully recovered. The outcomes in the patients infected with fully sensitive organisms and with organisms resistant to streptomycin only, although not significantly better, were nearly twice as good; this occurred even though none of the patients infected with organisms resistant to isoniazid only were coinfected with HIV, whereas, in the other groups of patients, 16.7%–35.7% were coinfected. The lack of HIV-infected patients among those infected with organisms resistant to isoniazid only would bias the results toward better survival, because death is independently associated with HIV infection.

Although it is possible that rifampin exerts some effect—especially early during the course of disease, when drug penetration into the CSF is better—attributing significant benefit to rifampin and discounting a possible contribution of isoniazid is a leap of faith. As Thwaites et al. suggest, isoniazid should not be stopped when resistance is identified; moreover, additional drugs need to be considered for patients who do not respond to therapy. Because the numbers of patients in Thwaites et al.’s groups were small and because there was considerable variability within groups with regard to HIV status, drug susceptibility, and neurological status, the study lacks the statistical power to support the authors’ conclusion that outcomes in patients infected with organisms resistant to isoniazid who are given a standard regimen are as good as those in patients infected with fully sensitive organisms. The contribution of streptomycin resistance, especially combined with isoniazid resistance, as well as the impact of HIV infection are unclear.

TBM remains a serious disease with disastrous consequences, despite chemotherapy and supportive therapy. The work done by Thwaites et al. in conducting this large prospective study adds much of importance to our knowledge. Additional information is needed to identify the best treatment regimens and management strategies. More-detailed information from this cohort on the drug resistances of the infecting organisms and the HIV status of the patients will be important to have. Information on the MICs of the isolates and
analysis of whether they correlate with response to therapy is also important, as is analysis of whether CSF parameters correlate with HIV status. Although the numbers of patients in the groups are too small to provide the statistical power needed to reach firm conclusions on these matters, preliminary information may help to focus future studies and formulate questions. Isoniazid should continue to be part of the treatment regimen when the detected resistance is of a low level. Additional drugs, especially the fluoroquinolones, would likely add important therapeutic benefit, and high-resource countries should consider using them as supplements to a standard regimen.

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References