Safety of the Rifampin and Pyrazinamide Short-Course Regimen for Treating Latent Tuberculosis Infection

To the Editor—The recent article by Cook et al. [1], wherein they compared the outcomes of treating latent tuberculosis infection with short-course regimens of either rifampin and pyrazinamide (RZ) or rifampin alone versus isoniazid, deserves further comment. The investigators’ careful monitoring of the Pitt County Health Department (Greenville, NC) patients treated with these 3 regimens, plus their analysis of 5 years of treatment-outcome data, complements our previous reports [2–4].

First, although not specifically calculated in their article, the rate of hospitalization for liver injury among the patients receiving RZ was 1 in 291 persons (3.4 cases per 1000 patients), in spite of pre-selecting away from the RZ regimen those patients who might have been at greater risk for liver injury. This rate is similar to our reported point estimate of 3.7 cases per 1000 patients initiating RZ, which was determined from a national survey that included a larger denominator of initiations of RZ treatment (n = 8087) [3]. No hospitalizations occurred among the Pitt County patients treated with rifampin or isoniazid. Also, although the authors detected no RZ-associated fatalities among the 291 patients who initiated RZ in their study, the study lacked sufficient sample size to measure a fatality rate if it was in the range of the reported rate of 0.9 cases per 1000 patients [3].

Cook et al. [1] found indistinguishable rates of liver injury for patients receiving either of 2 short-course regimens (RZ or rifampin) and patients receiving isoniazid. Given the history of RZ-associated hepatotoxicity and the estimated low rate of liver injury for rifampin [5–9], a more specific analysis would be to estimate the liver-injury rate only for persons who received RZ. Calculated from the data in the report, the observation of alanine aminotransferase levels that were >5 times the upper level of normal occurred 19 times among 291 persons who initiated RZ therapy (65 cases per 1000 patients [6.5%]). This rate for the group receiving RZ is not only greater than the rate for the group receiving isoniazid (6.5% versus 2.0%; \( P = 0.04 \), by \( \chi^2 \) test), but it is also greater than a previous estimate of 25.6 cases per 1000 initiations of RZ [3].

We agree that the study by Cook et al. “provides a more realistic picture of the true toxicity of this regimen” [1, p. 274]. Thus, we question advocating the use of RZ despite the high observed rates of adverse events, even with intensive monitoring. Surveillance data indicate that RZ-associated fatalities continued despite revised recommendations for increased monitoring of patients [4]. Given the treatment options, the risk of liver injury outweighs the benefits of the RZ regimen.

The 2003 recommendation to generally not use RZ for the treatment of latent tuberculosis infection [2] reflected a consensus recommendation by a panel of experts. The data-driven guidance from the Centers for Disease Control and Prevention and the American Thoracic Society was endorsed by the Infectious Diseases Society of America [2–4]. The preferred regimen is 9 months of daily or biweekly isoniazid therapy, with an alternative of 4 months of daily rifampin therapy [2]. Contrary to the authors’ interpretation, their findings reinforce the Centers for Disease Control and Prevention and the American Thoracic Society’s recommendation that RZ should generally not be offered to persons with latent tuberculosis infection [2].

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an understestimation of the actual incidence of hepatotoxicity in patients treated with INH.

In our cohort, none of the patients who developed hepatotoxicity because of PZA-RIF died. In fact, liver functions returned to normal in all patients when either PZA alone or both drugs were discontinued. We are increasingly using the 4-month regimen of rifampin to treat our patients with LTBI, because the hepatotoxicity is low and the completion rates are high for this regimen [7].

The authors from the Centers for Disease Control and Prevention would have us believe that treatment of LTBI is a choice between good (INH) and evil (PZA-RIF). Would that the argument were that simple. Our goal is for patients to complete therapy with whatever regimen is chosen. Given the greater likelihood of completing the short-course regimens (PZA-RIF for 2 months and RIF for 4 months) and the self-limited hepatotoxicity (in our hands) of the PZA-RIF regimen, we will continue to use both regimens in selected patients.

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References


Prevalence of Antibodies against Rubella Virus in Spain

To the Editor—Hyde et al. [1] report the results of a prevalence study of rubella immunity levels in the US population. In relation to their findings, we present our experience in a European country. The importance of the strategy of anticipating rubella revaccination, improved surveillance, and the implementation of specific vaccination programs against rubella addressing susceptible groups needs no emphasis [2, 3]. Recommendations by committees of experts and the prevailing childhood immunization schedules are unanimous in including the above-mentioned strategies [4]. In this context, ser-