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Needed: New and Better Tools to Combat Latent Tuberculosis Infection

Henry M. Blumberg, MD

Emory University School of Medicine Atlanta, GA 30303

Treatment of latent tuberculosis infection (LTBI) is a major strategy for tuberculosis control in the United States, Canada, and selected resource-intensive countries (1, 2). Given the decline in tuberculosis cases in the United States since 1992, interest in treating patients with LTBI is renewed in order to eliminate the large reservoir of individuals at risk for progression to tuberculosis (1, 3). The Centers for Disease Control and Prevention, such professional organizations as the American Thoracic Society and the Infectious Diseases Society of America, and others (1–3) recommend targeted testing of persons at increased risk for tuberculosis and provision of therapy for LTBI after active tuberculosis disease has been excluded. Persons at greatest risk for progression to active tuberculosis disease after infection with *Mycobacterium tuberculosis* include those with HIV infection (the greatest single risk factor for progression) or recent tuberculosis infection, immigrants with LTBI from high endemic areas (especially within their first year in the United States), and those with LTBI and selected underlying illnesses (for example, silicosis, diabetes mellitus, chronic renal failure, some malignant conditions, and immunosuppressive medications) (1, 3).

A major limitation to this strategy is poor acceptance and adherence to treatment regimens for LTBI (typically <50%) (4). Poor adherence is not surprising because treatment is arduous (9 months of isoniazid therapy is the preferred regimen [1]) and patients have no symptoms of infection. There was initial excitement about a 2-month, short-course regimen of rifampin and pyrazinamide for the treatment of LTBI, which was as efficacious as isoniazid in a narrowly defined HIV-infected study sample and had better adherence (5). However, when applied to the general population of patients with LTBI, rifampin–pyrazinamide led to an unacceptably high rate of severe hepatotoxicity and death (the estimated mortality rate was 1 in 1000 uses), and the recommendation to use this short-course regimen was subsequently withdrawn (6).

Four months of rifampin therapy is a recommended alternative to isoniazid for treating LTBI (1). It has been most commonly used among patients who are intolerant of isoniazid or are known to have been infected with *M. tuberculosis* strains that are resistant to isoniazid but susceptible to rifampin. Only 2 randomized trials have been on LTBI, and only 1 of these assessed efficacy. Thus, data are limited. Among patients in Hong Kong with silicosis and LTBI, 3 months of rifampin was similar in efficacy to other regimens (6 months of isoniazid and 3 months of isoniazid plus rifampin) and more efficacious than placebo (7). Therefore, the multicenter, open-label, randomized study in this issue by Menzies and colleagues (8), which compared 4 months of rifampin therapy with 9 months of isoniazid therapy for LTBI, is an interesting and welcome addition to the literature. In the study, carried out in Canada,

Requests for Single Reprints: Henry M. Blumberg, MD, Division of Infectious Diseases, Emory University School of Medicine, 49 Jesse Hill Jr. Drive, Atlanta, GA 30303; henry.m.blumberg@emory.edu..

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Brazil, and Saudi Arabia, 427 and 420 persons with LTBI were randomly assigned to isoniazid therapy and rifampin therapy, respectively. Given the rate of progression from LTBI to active tuberculosis (5% to 10% lifetime risk in patients without HIV infection), the sample size was too small to assess efficacy. The primary end point was adverse effects, in particular more severe hepatotoxicity (grade 3 to 4), because both isoniazid and rifampin can cause hepatotoxicity. There were no significant differences between rifampin and isoniazid in drug-related adverse events. However, grade 3 (aspartate aminotransferase [AST] and alanine aminotransferase [ALT] levels 3 to 10 times the upper limit of normal [ULN] plus symptoms or 5 to 10 times ULN with no symptoms) or grade 4 (ALT and AST levels >10 times ULN) hepatotoxicity was significantly less common among patients in the rifampin group (0.7%) than among those in the isoniazid group (3.8%) (risk difference, -3.1% [95% CI, -1% to -5%]). It is unclear how many patients had symptoms associated with increases in levels of AST or ALT. The authors also found that patients in the rifampin group were significantly more likely to complete treatment (78% for rifampin vs. 60% for isoniazid).

The current recommendations for treatment of LTBI (1, 6) often seem more faith-based than evidence-based. Despite substantial data on the use and efficacy of isoniazid for treating LTBI (>20 randomized, controlled trials involving >100 000 persons [4]), the recommendation for 9 months of isoniazid (1) does not come directly from any randomized trials (for example, comparing 9 months with 6 or 12 months of therapy), but from reanalysis of data collected 50 years ago (9). Use of 4 months of rifampin as the preferred regimen for treatment of LTBI is not indicated on the basis of Menzies and colleagues' findings. Very limited data are available on the efficacy of rifampin (7) for treating LTBI, with most reports being small case series or programmatic evaluation of the use of rifampin in nonrandomized studies with sample sizes that are inadequate to evaluate efficacy (10 – 12).

The evidence from Menzies and colleagues' study (8) suggesting that rifampin is less hepatotoxic than isoniazid is consistent with a very limited body of evidence in other reports that had small sample size or nonrandomized study design (7, 12). However, the present study (8) does not resolve all questions about safety, and additional and larger studies are needed, especially in light of the recent unfortunate experience with rifampin plus pyrazinamide for LTBI. Menzies and colleagues excluded patients with potential drug interactions with rifampin. Potential study limitations include that it was open-label and not blinded. Investigators measured AST and ALT levels routinely at baseline and 1 and 2 months after treatment rather than monthly throughout the study. The article does not say if study participants who were at increased risk for hepatotoxicity had monthly ALT and AST levels measured, as recommended by current guidelines (1, 2). In addition, almost 20% of patients had missing ALT or AST values during the first 2 months of the study. Finally, the study was too small to measure the frequency of very serious but rare rifampin-related side effects that are thought to be immune-mediated, such as renal failure, thrombocytopenia, hemolytic anemia, or thrombotic thrombocytopenic purpura (13).

The severe hepatotoxicity associated with the combined use of rifampin and pyrazinamide to treat LTBI has been suggested to be due to pyrazinamide (14); however, more data are needed on potential rifampin toxicity when used for treatment of LTBI, given the potential impact when thousands, tens of thousands, or hundreds of thousands of patients are treated. Furthermore, rifampin is not the perfect or ideal drug for the treatment of LTBI given that a major limitation is the many drug interactions associated with its use. Rifampin is a potent inducer of cytochrome P-450 oxidative enzymes as well as the P-glycoprotein transport system, both of which lead to enhanced clearance of important drugs (15). Examples of well-documented, clinically significant interactions include warfarin, oral contraceptives, cyclosporine, azoles, clarithromycin and trimethoprim-sulfamethoxazole, digoxin, calcium

channel blockers, statins, oral hypoglycemic agents, benzodiazepines, and HIV-related protease inhibitors (15).

Menzies and colleagues state that “drug-induced hepatotoxicity [from isoniazid] is difficult to detect and can be fatal.” Early detection of hepatotoxicity can be difficult if patients are followed only for clinical symptoms, as the current guidelines (1) recommend for most patients. However, obtaining monthly ALT and AST levels in adults receiving isoniazid therapy is a sensitive and effective mechanism for ensuring that treatment of LTBI is delivered safely by detecting substantial hepatotoxicity before clinical symptoms arise (16) and discontinuing therapy when grade 3 or 4 hepatotoxicity occurs. The risk for drug induced hepatitis from isoniazid was higher in Menzies and colleagues' study than in many but not all previous reports. A large study conducted by the U.S. Public Health Service involving nearly 14 000 participants, as well as a more recent multicenter study, reported rates of isoniazid-induced hepatotoxicity in the range of 1% (14, 17). Mortality rates associated with use of isoniazid for LTBI are reported in the range of 0 to 0.3 death per 1000 persons (median, 0.04 death per 1000 persons) (6). These are preventable with biochemical monitoring.

Menzies and colleagues rightly conclude that a large scale trial is indicated to assess the efficacy of rifampin monotherapy for the treatment of LTBI. Other regimens for the treatment of LTBI, such as 3 months of isoniazid plus rifampin therapy (which has been evaluated in 3 randomized trials [8, 18, 19] but never recommended for use in North America by public health officials [1, 2]), also need to be studied. The best hope on the horizon for a shorter treatment regimen for LTBI rests with the Centers for Disease Control and Prevention Tuberculosis Trials Consortium Study 26, which is evaluating weekly rifapentine (a long-acting rifamycin) plus isoniazid for 12 weeks by directly observed therapy versus daily self-administered isoniazid for 9 months (20). The enrollment target of 8000 patients was reached in February 2008, and study results are anticipated in late 2010. At least 11 million persons have LTBI in the United States (21), and about 300 000 to 400 000 persons start therapy for LTBI each year, resulting in prevention of between 4000 to 11 000 active tuberculosis cases (22). Despite these substantial numbers, public funding of research to develop the new tools needed to further tuberculosis control by addressing LTBI is woefully inadequate. For the first time in more than 30 years, several promising new agents for treatment of tuberculosis disease are being evaluated in clinical trials (23). We need continued advocacy, scientific and public health leadership, and resources to further the research agenda for new, safe, short, effective, and evidence-based regimens for the treatment of LTBI.

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