

Rifampin and Pyrazinamide for Latent Tuberculosis Infection: Clinical Trials and General Practice

Jussi Saukkonen

Pulmonary Center, Boston University School of Medicine, Boston, Massachusetts

(See the article by Gordin et al. on pages 561–5)

As the prevalence of active tuberculosis decreases in the United States, the focus on treatment of latent tuberculous infection (LTBI) has intensified. However, the standard 6–9-month course of isoniazid has been burdened with suboptimal rates of therapy completion and concerns about hepatotoxicity and infection with isoniazid-resistant organisms. These issues have spurred interest in alternative, shorter regimens [1].

One of these LTBI regimens, a 2-month course of rifampin with pyrazinamide (RZ), has achieved considerable controversy because of serious concerns about its safety. Initially, randomized studies involving HIV-infected individuals indicated that the regimen was safe, with no significant differences in hepatotoxicity, compared with a 6-month course of isoniazid [2, 3]. Gordin et al. [4] found that hepatotoxicity that was potentially life-threatening or led to treatment discontinuation was less common among patients treated with RZ than among those treated with 12 months of isoniazid. This study had

broad inclusion criteria; it enrolled substantial numbers of injection drug users who might have increased risks for hepatotoxicity, as well as individuals with baseline transaminase levels of up to 5 times the upper limit of normal. This study also reported equal efficacy for both LTBI treatment regimens in HIV-infected individuals. Subsequently, RZ was recommended for treatment of LTBI in HIV-infected individuals, and the recommendation was extended to HIV-uninfected individuals as an acceptable alternative regimen for isoniazid [1].

The ensuing experience with RZ in the HIV-uninfected population raised serious concerns regarding the hepatotoxicity of the regimen. Jasmer et al. [5] found that individuals treated with a 2-month course of RZ developed significantly more elevations in the alanine aminotransferase (ALT) level of grade III or higher (i.e., an ALT level of ≥ 250 U/L), compared with patients who were treated with a 6-month course of isoniazid, and RZ recipients were not more likely to complete the regimen. A nonrandomized trial reported significantly more elevations in the aspartate aminotransferase (AST) level of ≥ 160 U/L in patients who were treated with a 2-month course of RZ [6]. There were case reports to the Centers for Disease Control and Prevention that eventually totaled 48 fatalities and hospitalizations associated with RZ, which prompted revised rec-

ommendations that limited RZ prescription for treatment of LTBI. These recommendations included provision of no more than 2-week supplies of RZ per visit, exclusion of patients with liver disease or history of significant isoniazid hepatotoxicity, intensified monitoring of liver enzyme levels, and cautious use of RZ for persons who were taking concomitant hepatotoxic agents [7–9].

A retrospective surveillance study of patients treated with 2-month courses of RZ was launched in response to these events. The study found hospitalization and mortality rates of 3 hospitalizations and 0.9 deaths per 1000 treatment initiations [9]. These numbers are considerably higher than recent hospitalization and death rates for isoniazid of 0.1–0.2 hospitalizations and 0–0.3 deaths per 1000 treated [9]. Eleven deaths were reported among patients treated with 2 months of RZ, including the deaths of 2 HIV-infected individuals. Recommendations were revised to stipulate that RZ generally not be offered to patients for treatment of LTBI and certainly not to individuals with underlying liver disease or injury or who regularly ingest hepatotoxic agents. Monitoring of transaminase levels was recommended at 2-week intervals for persons prescribed RZ for treatment of LTBI. These recommendations were applied equally to HIV-infected and HIV-uninfected individuals [9], although the clinical

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Reprints or correspondence: Dr. Jussi Saukkonen, Pulmonary Center, Boston University School of Medicine, 80 E. Concord St., R-304, Boston, MA 02118 (jsaukkonen@lung.bumc.bu.edu).

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trial experience suggested that the rate of RZ-associated hepatotoxicity was not significantly greater than the rate of isoniazid-associated hepatotoxicity for HIV-infected individuals.

In this issue, Gordin et al. [10] provide additional data on hepatotoxicity from their initial treatment trial comparing isoniazid and RZ for treatment of LTBI in HIV-infected individuals. Their first report was limited to the occurrence of life-threatening and treatment-limiting hepatotoxicity, whereas the new report provides objective data in the form of information on grade III or higher elevations in the AST level, as well as other measurements of hepatotoxicity. This new data also allows for better comparisons with other studies done in the field. Grade III elevations of AST levels were no more common in the RZ group than in the isoniazid group, nor were other measurements of hepatotoxicity. Multiple regression analysis showed that increases in the AST level of ≥ 40 U/L were associated with older age, which was also previously identified as a risk factor for hepatotoxicity in the HIV-uninfected population [5]. The authors compare hepatotoxicity rates reported in studies of HIV-infected and HIV-uninfected individuals and find substantially higher rates among the latter. They conclude that, although 2-month regimens of RZ are unsafe for general use in the HIV-uninfected population, their data support use of this regimen for HIV-infected individuals who are not likely to complete a longer regimen [10]. However, 2 of the deaths associated with RZ therapy involved HIV-infected individuals. The authors recommend adherence to the most current updated recommendations regarding RZ, for use only under very specific conditions.

Several issues gnaw in the recent history of 2-month courses of RZ for treatment of LTBI. A common dilemma in interpreting the results of clinical trials is how far to generalize the findings of a study. In making such an assessment, consideration is given to how a study population

differs from larger groups potentially eligible for the treatment studied. Furthermore, particularly for interpreting serious adverse events, it is important to consider how general clinical practice may differ from that under study conditions. Cofactors that may contribute to liver injury, such as preexisting liver disease, concomitant medications being used, alcohol consumption, and the coincidental occurrence of viral hepatitis, are not always available to aid in the interpretation of clinical trials. In general clinical practice, these hepatotoxicity cofactors may be more widespread and less appreciated.

The cause of the evident disparity in the rates of clinically significant hepatotoxicity in HIV-infected and HIV-uninfected individuals remains unclear. The pathogenesis of RZ-associated hepatotoxicity is not understood, but one may speculate that immune-mediated injury could be attenuated in persons with HIV infection, even in the face of moderately high CD4 cell counts [11], or with reduced bioavailability in patients with AIDS [12] might be responsible. Some have hypothesized that RZ-associated high-grade hepatotoxicity is more common when RZ is prescribed as treatment for LTBI, in contrast to that seen with RZ when prescribed as part of 4-drug therapy for active TB. This might be related to relative immunodeficiency [13], although it is not clear that such defects are relevant. Some have suggested that isoniazid may exert a protective effect when given with RZ, perhaps through decreased bioavailability of rifampin [14]. However, the major offending agent has been believed to be pyrazinamide [5]. Rifampin has been implicated in increasing the likelihood of liver injury when used in combination with isoniazid or other antituberculous agents [15]. Whether this is, in fact, the case with RZ is unclear. Overall, it is difficult to precisely determine graded hepatotoxicities seen in active TB treatment trials, because such data have often been vaguely reported or include low-grade hepatotoxicity. Hepatotoxicity of grade III or higher seen in

HIV-uninfected individuals [5, 6] is within the range that has been reported for treatment of TB with multiple-drug regimens [16–22]. More striking is the severity of hepatotoxicity, with resulting death and hospitalizations in both HIV-infected and HIV-uninfected individuals, associated with RZ in general clinical use, but not in clinical trials [2–6, 10]. In relation to isoniazid for treatment of LTBI, RZ is more hepatotoxic in the HIV-uninfected population, but in clinical trials of HIV-infected individuals, this does not appear to be the case.

Given these aggregate findings, it seems prudent to restrict use of RZ for treatment of LTBI to very specific instances in which the use of isoniazid is not feasible; the risks can be minimized and are not expected to exceed the benefit of the treatment [10]. Rifampin, with or without isoniazid, for 4 months constitutes an often-used alternative regimen [1]. A three-month regimen of once-weekly isoniazid and rifapentine is currently under investigation by the TB Trials Consortium to determine safety and efficacy for treatment of LTBI. There is clearly a need for shorter, safe, and effective regimens for LTBI that can be used with relative ease in the general population.

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