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A Balancing Act: Finding the Right Dose of Pyrazinamide to Treat Tuberculosis

Pyrazinamide (PZA) is a drug with potent activity against *Mycobacterium tuberculosis*, and its addition to treatment paved the way for modern "short-course" treatment of pulmonary tuberculosis (TB) (1). Despite the fact that PZA has been a core component of anti-TB treatment for more than 50 years, optimal dosing is still not understood. Pharmacokinetic modeling studies suggest that significant variability exists in PZA exposure based on sex, race, food intake, and concomitant drugs, and that higher doses of PZA may be needed to increase efficacy (2, 3). Low PZA exposure has been associated with a longer time to culture conversion and poor TB treatment outcomes (4, 5). At the same time, higher doses are associated with increased intolerance (6). Furthermore, pyrazinamide is the first-line anti-TB drug most commonly associated with discontinuation due to adverse effects (7). Optimizing PZA dosing has the potential to maximize efficacy while minimizing the harms of TB treatment.

In this issue of the *Journal*, Xu and colleagues (pp. 1358–1369) analyzed the pharmacodynamics of PZA dosing in Tuberculosis Trials Consortium Study 31, a phase III randomized trial comparing two 4-month regimens containing high-dose rifapentine versus standard 6-month therapy in patients aged ⩾12 years with pulmonary TB (8). To date, this is the largest study to analyze the relationships among PZA dosing, exposure, and important safety/efficacy outcomes, with close to 7,000 plasma samples among 2,200 participants. PZA was dosed according to weight in all arms, with a dose range between 1,000 and 2,000 mg/d, corresponding to approximately 18–27 mg/kg total body weight. The authors then developed and validated models evaluating PZA pharmacokinetics and the relationship between pharmacokinetics and efficacy and safety among participants.

The first key finding was that PZA exposure was highly variable, with decreasing bioavailability as the dose increased and increased overall exposure (measured by area under the curve) as the dose increased, despite increasing average body weight in the dose bands. This observation agrees with prior work (2, 3, 5) and supports the authors' contentions that weight-based dosing of PZA makes little sense from a pharmacokinetic perspective and a fixed dose should be used.

The second key finding was that greater PZA exposure was associated with lower risk of TB-related unfavorable outcomes in the standard regimen, but not in the high-dose rifapentine regimens. The correlation between greater PZA exposure and greater antimicrobial efficacy in the standard-therapy arm is also concordant with prior work (2, 5, 9), but the lack of a correlation in the high-dose rifapentine arms is novel and interesting, reaffirming the importance of considering the entire regimen when evaluating pharmacodynamics of TB drugs rather than just a single drug in isolation.

The third key finding was that increasing PZA exposure was associated with an increased risk of grade 3 or higher adverse events in two of the three treatment groups (control and rifapentine/moxifloxacin) and an increased risk of treatment discontinuation due to an adverse event. The association between increased PZA exposure and intolerability was also consistent with prior reports. Interestingly, a significant association between hepatotoxicity and higher PZA exposure was reported, which differs from prior studies of PZA using this dose range that found no such association (2, 3, 5, 6).

The exposure-efficacy and exposure-safety data were used to establish therapeutic windows. For the 6-month standard treatment group, 95% durable cure was used as the lower threshold and an 18% probability of a grade 3 or higher adverse event was used as the upper threshold of the window. For the 4-month rifapentine/moxifloxacin group, the same probability was used to set the upper threshold of the window, but no TB-related unfavorable outcomes were observed to inform the selection of the lower threshold. Based on these parameters, the authors identified that flat dosing of PZA at 1,000 mg achieved higher proportions of participants within the therapeutic windows than weight-banded dosing and 1,500-mg dosing.

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On the whole, the Xu and colleagues' study is a thoughtful analysis of a large, high-quality dataset that confirms much of what we knew before about PZA pharmacodynamics. Although the study is limited by relatively low event rates for some key toxicities (e.g., hepatotoxicity) and a somewhat arbitrary therapeutic window, it provides several key insights that illuminate a pathway to the optimal use of PZA in TB treatment. First, the use of a fixed PZA dose rather than weight-banded dosing simplifies treatment and makes good pharmacokinetic sense. Second, the optimal fixed dose is likely to vary with the rest of the regimen. A lower PZA dose, which presumably would be better tolerated, may be the best choice in a more potent background such as that provided by high-dose rifapentine. Conversely, a higher PZA dose, which presumably would be more effective, may be necessary to optimize a less potent regimen that may have other attractive features such as favorable drug interactions with antiretroviral agents. Third, the choice of parameters to define a therapeutic range based on safety and efficacy should be informed by a combination of patient preferences and formal decision analysis modeling to delineate probable rates of unfavorable TB events, adverse effects, and costs associated with different dose regimens. Fourth, diversity is important in TB clinical trials. In this case, only 12% of the study participants were of Asian ethnicity, and, as previously mentioned, this population is at higher risk for PZA toxicity; the appropriate therapeutic window may differ according to the population being treated. Additionally, only 8% of the cohort had HIV infection and 3% had diabetes; these are important subgroups for whom PZA pharmacodynamics may differ.

Although some would argue that PZA is an old and relatively poorly tolerated drug, it is likely to remain a cornerstone of TB treatment for the foreseeable future, especially because it seems highly potent in combination with new drugs such as bedaquiline (10). The study of Xu and coworkers suggests that a combination of pragmatic trials comparing flat PZA doses and embedding pharmacodynamics substudies into trials of novel regimens will be the best way to finally find the right dose of pyrazinamide. ■

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