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Pyrazinamide in Treatment of Infection With Bacillus Calmette–Guerin; Does It Work?

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Dear Editor,

In 2011, World Health Organization (WHO) reported the total world incidence of tuberculosis (TB) to be estimated at 125 per 100,000 people, equivalent to 8.7 million; moreover, 12% to 14% of these cases (i.e. one million to 1.2 million people) were HIV positive who were mainly African (79% of the total TB/HIV co-infected individuals) (1). Global expansion of TB burden, and prevention strategies are two powerful forces in mycobacterial infection control. Although administration of Bacillus Calmette–Guerin (BCG) vaccine at birth is the mainstay of prevention in Iran, lack of information on the immune state of vaccinees may lead to rare cases of disseminated BCG infection. Disseminated BCG infection may occur in different genetic disorders. Pedraza-Sanchez et al. reported two cases from Mexico with a point mutation in the *IL12RB1* gene and fatal outcome from BCG infection (2). Low level resistance to isoniazid and resistance to pyrazinamide are the main characteristics of BCG strains (3). Fahimzad et al. suggested a new issue on pyrazinamide concentration and its probable therapeutic effect on these hard-to-treat patients (4). Guidelines on treatment and drug management of BCG infection are insufficient (5). Therefore, pyrazinamide still can be a good candidate in BCG infection treatment. Pyrazinamide is a synthetic antimycobacterial agent with anti-*Mycobacterium tuberculosis* activity while *Mycobacterium bovis* is resistant to this drug (6). Fahimzad et al. study on BCG strain ATCC 1173 p and three samples of *M. bovis* isolated from children with adenitis showed *M. bovis* susceptibility to pyrazinamide with high concentrations (50 μg/mL) added to the culture plates in combination with other anti-mycobacterial agents, in spite of its initial resistance (4). Demonstrating high concentration of serum pyrazinamide without toxic effects may give a valuable opportunity to add high-dose pyrazinamide in treatment of BCG infections. Pyrazinamide is administered orally, 15 to 30 mg/kg once daily. The Center for Disease Control (CDC) does not recommend exceeding 2 g per day when given as a daily regimen (7). Targeting on higher dose of pyrazinamide to treat difficult mycobacterial infections such as infection with BCG needs evaluation of plasma concentration of this drug to confirm the drug efficacy. Plasma concentration of anti-TB drugs depends on many factors; therefore, achieving high serum concentration of these drugs based on the recommendation is an important target of investigation. In a study by Fahimi et al. (5) in Masih Daneshvari Hospital, Tehran, Iran, in 2013, the median peak plasma concentrations, i.e. C (max), of isoniazid, rifampin, and pyrazinamide among 60 adults with pulmonary TB two and six hours after drug administration were 2.5, 4.0, and 43.6 μg/mL, respectively; 81% of the patients had drug plasma concentrations lower than the target ranges for at least one administered drug. Moreover, 49.1%, 92.5%, and 8.7% of the patients had low concentrations of isoniazid, rifampin, and pyrazinamide. Low concentrations of anti-TB drugs are related to drug resistance and treatment failure. These results indicated that rifampin concentrations were below the reference range in most patients, while pyrazinamide concentration was within the target range of the standard doses (5). Roy V reported the blood concentration of pyrazinamide based on Revised National Tuberculosis Control Program of India (RNTCP) in 20 children in the age group of five to 12 years attending outpatient TB clinic of a tertiary hospital. Area under the curve (AUC) to minimum inhibitory concentration (MIC; 25 μg/mL) in children were lower than that recommended for pyrazinamide in adults. The results indicated that lower blood concentrations was attained in children receiving pyrazinamide doses under the existing weight band system of RNTCP of India. The weight bands should be revised and dose recommenda-

tions should be based on pharmacokinetic and efficacy data in children (8). Therefore, as Fahimzad et al. declared, increasing the number of cases and evaluation of in vivo performance of pyrazinamide in future studies is strongly recommended (4).

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