

Correspondence

A randomised controlled trial of high-dose isoniazid adjuvant therapy for multidrug-resistant tuberculosis

The findings by Katiyar et al. in a recent issue of the *Journal* that the adjuvant use of high-dose isoniazid (INH) significantly improves results when retreating multidrug-resistant tuberculosis (MDR-TB) is a welcome finding.¹ An earlier non-randomized trial by Petty et al. found similar superior results when high-dose isoniazid (INH) was added to a retreatment regimen of ethionamide (ETH) and pyrazinamide (PZA).² In a discussion of this issue, I presented a line of reasoning that the superior results found by Petty et al. may have been specific for an ETH-containing regimen, as it is known that strains with INH resistance have an unusual pattern of cross-resistance with ETH.³ Low-grade INH-resistant organisms are often resistant to ETH, and high-grade INH resistance organisms are more susceptible to ETH.⁴ Therefore, adding high-dose INH kills the low-grade INH-resistant organisms, leaving only high-grade INH-resistant organisms that are more susceptible to ETH, resulting in better clinical results.³ Less compelling evidence was presented showing that there is a similar process of cross-resistance between INH and PZA.³ Katiyar et al. added high-dose INH to regimens containing prothionamide, kanamycin, levofloxacin, cycloserine and PAS.¹ Prothionamide and ETH are very similar in structure, but it is unknown to me if they have the same patterns of cross-resistance with INH.

The issue is important, because clinicians need to know whether or not to add high-dose INH to all retreatment regimens or only to retreatment regimens containing specific drugs. A recent article by Morlock et al., which described the genetic mechanism for the INH-ETH cross-resistance patterns, may prove to be one line of investigation that could help answer this question.⁵

Note: Reference #28 in the article by Kariyar et al. to one of my publications is apparently an error, since it addresses an entirely different issue.

THOMAS MOULDING
*Division of Respiratory and Critical Care
Physiology and Medicine
Harbor-UCLA Medical Center
Torrance, California, USA
e-mail: tmoulding@earthlink.net*

References

- 1 Katiyar S K, Bihari S, Prakash S, Mamtani M, Kulkarni H. A randomised controlled trial of high-dose isoniazid adjuvant therapy for multidrug-resistant tuberculosis. *Int J Tuberc Lung Dis* 2008; 12: 139–145.
- 2 Petty T I, Mitchell R S. Successful treatment of advanced isoniazid- and streptomycin-resistant pulmonary tuberculosis with ethionamide, pyrazinamide, and isoniazid. *Am Rev Respir Dis* 1962; 86: 503–512.
- 3 Moulding T S. Should isoniazid be used in retreatment of tuberculosis despite acquired isoniazid resistance? *Am Rev Respir Dis* 1981; 123: 262–264.
- 4 Canetti G, Kreis B, Thibier R, Gay P, Le Lirzin M. Current data on primary resistance in pulmonary tuberculosis in adults in France. 2nd survey of the Centre d'Etudes sur la Resistance Primaire: 1965–1966. *Rev Tuberc Pneumol (Paris)* 1967; 31: 433–474.
- 5 Morlock G P, Metchock B, Sikes D, Crawford J T, Cooksey R C. *EthA*, *inhA*, and *katG* loci of ethionamide-resistant clinical *Mycobacterium tuberculosis* isolates. *Antimicrob Agents Chemother* 2003; 47: 3799–3805.

In reply

We thank Dr Moulding for his insightful comments on the implications of our work.¹ He raises an extremely pertinent question regarding the possibility of cross-resistance of isoniazid (INH) resistant strains with prothionamide (PTH). All the subjects in our study received a standardized course of second-line anti-tuberculosis treatment that included PTH, and we do not have laboratory data on the PTH resistance profile of these patients. The clinical protocol of our trial did not permit us to compare INH-resistant MDR-TB patients who did or did not receive PTH. Therefore, it will not be possible to directly answer the question raised from our study data. While generalizing the results of our trial one should therefore bear in mind that the effectiveness of high-dose INH adjuvant therapy was observed in the context of a PTH-containing regimen for second-line treatment. Generalization to other regimens will need more laboratory and clinical work.

Regarding reference 28 being misquoted, we would like to clarify that the four references included together in our article were categorized as 'other experiences'. We certainly could have been more explicit, but what we wanted to convey was that INH has value in both preventing and treating MDR-TB. We again thank Dr Moulding for these very helpful comments.

S. K. KATIYAR*
S. BIHARI*

S. PRAKASH*†
M. MAMTANI†
H. KULKARNI†

*Department of Tuberculosis &
Respiratory Diseases
Ganesh Shankar Vidyarthi Memorial
Medical College
Kanpur

†Lata Medical Research Foundation
Nagpur, India
e-mail: hemant_kulkarnius@yahoo.com