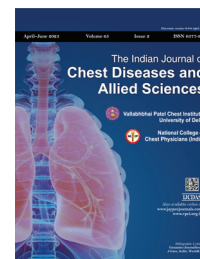


Treatment of Isoniazid-resistant Tuberculosis: Need to Revisit

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Dear Editor,

Treatment of drug sensitive and multidrug-resistant (MDR) Tuberculosis (TB) is well standardized and practiced all over the world.^{1,2} However, the management of Isoniazid (INH) mono resistance is a matter of debate. A National drug sensitivity survey conducted by the government of India between July 2014 and May 2016 showed that 11.06% of newly diagnosed and 25.09% of previously treated patients have INH mono-resistant disease in India.³

Center for disease control (CDC) and the American Thoracic Society (ATS) in the year 1986 recommended 12 months of Rifampicin, Ethambutol, and Pyrazinamide (REZ) for the management of INH-resistant TB.⁴ Wallace Fox in his review discussed data from several British Medical Research Council (BMRC) associated studies on short-course chemotherapy conducted across the world. He analyzed the patients with primary drug resistance to INH, treated with Isoniazid, Ethambutol, Rifampicin, and Pyrazinamide (HERZ) for 2 months, followed by Isoniazid, Rifampicin (HR) for four months. He observed similar efficacy of 6-month HERZ/HR in both drug-sensitive and drug-resistant TB at the end of treatment. However, relapses were slightly more common (3% vs 2%) among those with drug resistance disease.⁵

A recent World Health Organization (WHO) document on the management of drug-resistant tuberculosis recommended 6 months of Ethambutol, Rifampicin, Pyrazinamide, and Fluoroquinolone (ERZQ) for INH-resistant Tuberculosis. This may be extended to a total of 9 months in certain situations. This recommendation was conditional with the low level of evidence. The guideline development group (GDG) did not find any randomized control trial (RCT)/cohort study about the management of INH-resistant Tuberculosis. The guideline development group could not suggest a regimen for INH resistant TB and recommended that individual patient data in INH-resistant disease from different regimen may be analyzed.²

We reviewed the records of our patients who completed treatment for INH-resistant TB at our center between January 2022 and December 2022. A total of 10 patients received treatment for INH-resistant disease. All these patients were treated with HERZ for a duration of 12 months. Out of 10 patients, 8 patients completed HERZ for 12 months with a successful outcome. The mean duration between treatment initiation and completion of 12 months of treatment was 400 days. One patient defaulted at 6 months of follow-up due to a road traffic accident. He later resumed treatment after an interruption of 2 months and is doing well presently. Another patient had clinical/radiological deterioration at 6 months

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of follow up and sputum culture for Mycobacterium turned out positive and resistant to both rifampicin and isoniazid. This patient has been shifted to MDR regimen.

Patient found to have MDR disease at 6 months could be due to acquiring additional drug resistance but seems less likely as a patient was on optimum dose and regular treatment. We feel this patient might be one of those where line probe assay (LPA) fails to pick the resistance to Rifampicin. Line probe assay has a sensitivity of 93.1% for detecting Rifampicin resistance.⁶ If we consider the missing of Rifampicin resistance in the above-mentioned patient who failed on HERZ, it will give stronger evidence in favor use of HERZ for 12 months in patients with INH-resistant disease.

Stagg et al.,⁷ compared the efficacy and toxicity of 12 months of Isoniazid, Rifamycin, Pyrazinamide, Ethambutol alone and with fluoroquinolone in INH-resistant TB. They observed similar effectiveness with fewer adverse effects of the regimen without fluoroquinolone.

We also searched the outcome of INH mono-resistant tuberculosis patients who were treated with Rifampicin, Ethambutol, Pyrazinamide, and Levofloxacin (REZLf) for a period of 6–9 months under a national TB eradication program at a local TB clinic during the year 2022. Records of a total of 55 patients were available for analysis. Out of 55 patients, seventeen were reported as cured, 24 completed treatment, five patients died during treatment, and an additional five patients were lost to follow up. The treatment regimen was changed in 4 patients.

Our observations support the use of 12 months of HERZ in patients with INH mono-resistant TB compared to WHO recommended regimen (6–9 months REZLf). Further, we also suggest that sputum for Mycobacterium culture should be submitted for all those

who have INH-resistant disease, and if found to have suboptimal clinic-radiological response on follow-up, then culture growth can be considered for repeat LPA testing to pick missed MDR at earliest. However, having a multicenter cohort study is desired to verify these observations.

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