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Editorial

# Isoniazid Mono-resistance: Implications on Tuberculosis Control

Resistance to anti-tuberculosis drugs has always been a hurdle in tuberculosis (TB) control. Mono-resistance to anti-tuberculosis drugs is nothing new. Soon after streptomycin was introduced for clinical use in 1944, there was genesis of resistance to the drug, and subsequently, other drugs were added leading to the era of combination drug therapy. Initially two-drug regimen was used and later on three-drug regimen was in use for a long period. In 1993, American Thoracic Society (ATS) recommended that in areas with high endemicity having prevalence of isoniazid (INH) resistance >2%, four-drug regimen should be given for treatment of TB.[1] Multi-drug resistant TB (MDR-TB) emerged as a problem in late 20th Century and with more than 480,000 patients per year globally, it is one of the greatest challenges to control TB. It is well accepted that patients with rifampicin resistance almost always have INH resistance as well. With this fact, in the context of MDR-TB, the focus has always been on rifampicin resistance, but isoniazid mono-resistance (IMR) has not received its due importance. It is presumed that four-drug regimen (Category 1) treatment is sufficient to take care of the IMR. However, it is evident that IMR has implications on response, duration of therapy and relapse rate of the disease.[2] Isoniazid mono-resistance has not been thought to be important in TB control and World Health Organization (WHO) global report does not mention about it. The reason remains simple that physicians do not really test the samples for INH resistance. A recent model-based analysis revealed that if TB treatment practices in India remain unchanged over the next 20 years, there will be a 47% increase in INH resistance and 152% increase in MDR-TB cases.[3]

Globally, INH resistance has been reported to be 10.3% in new cases and 27.7% of treated cases. From India also a high percentage of INH resistance (15.4%-23.4%) is being reported.[4,5] In a prospective study from Mexico, 9.8% TB patients had IMR and these patients had higher treatment failure and death due to TB.[6] Poor treatment outcomes in patients with IMR-TB has also been reported in a retrospective study from Andhra Pradesh.[7] INH mono-resistance not only leads to poor response and genesis of MDR, it also leads to higher mortality as reported in a study from Thailand.[8]

To assume that treatment with four-drug combination regimen will cure IMR cases can be dangerous. Until recently, WHO had advised similar therapy for IMR cases and drug-sensitive TB cases. Clinicians or researchers have no interest to look at the outcomes of these cases as funding agencies and researchers have always focussed on MDR- and XDR-TB treatment only. Till now, the treatment regimens for IMR-TB have not been evaluated prospectively and most of the studies are retrospective analysis of clinical data. The only clinical trial which evaluated the treatment regimen efficacy for IMR-TB was conducted in India long time back and had shown favourable results with eight months of daily therapy.[9] A recent meta-analysis suggested that use of conventional WHO recommended regimen for the treatment of INH-resistant TB results in unfavourable outcomes.[2] The rates of unfavourable outcomes (failure or relapse, or both) were 15% and 4% for IMR-TB and drug-sensitive TB, respectively.[2] The risk of acquired drug resistance was 3.6% and 0.6% for IMR-TB and drug-sensitive TB, respectively. Treatment of IMR-TB with the WHO recommended regimen for new patients resulted in treatment failure, relapse, and acquired MDR in 11%, 10% and 8%, respectively.[2] Authors observed that use of standard first-line regimen in IMR cases could lead to 60,000 new MDR-TB cases per year. This highlights the fact that IMR-TB should not be treated the same way as drug-sensitive TB, especially in areas with high IMR prevalence, like India.

It is, therefore, essential to identify drug resistance pattern at baseline to determine appropriate treatment regimen. Clinically significant INH resistance most commonly occurs due to mutation in katG gene coding catalase-peroxidase enzyme which is essential for INH conversion to an active form. Mutations of inhA promoter gene is also associated with low level resistance to INH and also confers resistance to ethionamide.[10] The diagnosis of drug resistance in TB has always been difficult predominantly due to long time taken for mycobacterial growth on conventional solid culture media. Since the widespread use of liquid culture media, the time for culture and drug susceptibility testing has significantly reduced. Availability of molecular methods of drug resistance testing including GeneXpert and line probe assay (LPA) has further reduced the time to detect drug resistance.[11] National programme has endorsed use of LPA techniques that identify resistance to INH as well as rifampicin. Line probe assay can also identify high or low levels of resistance depending on whether the mutation involves katG gene or inhA gene. The only problem in performing LPA is that it can only be done when the diagnosis of TB has been confirmed by smear or culture methods. In principal, Revised National Tuberculosis Control Programme (RNTCP) has accepted both GeneXpert and LPA methods for the molecular diagnosis of drug resistance. The widespread use of GeneXpert has helped in the diagnosis of MDR-TB

but at the same time, INH mono-resistance is missed. This problem has large scale healthcare implications in India as treatment of IMR cases with standard regimen is going to create more cases of MDR-TB. At present, LPA facility in India (under programmatic as well as non-programmatic conditions) is sparse.

Revised National Tuberculosis Control Programme has made a progress and has recognised INH resistant TB as a separate entity. But the bottleneck remains the diagnosis of IMR, as the prevalence of IMR is high, and it becomes imperative to establish drug susceptibility pattern at the baseline though it may not be feasible under programmatic conditions. In all TB patients, samples should be sent for liquid culture and LPA (if smear positive). Line probe assay can also be performed on extra-pulmonary samples after liquid culture shows growth of *Mycobacterium tuberculosis* as it definitely reduces the time to diagnosis of drug resistance (2 days for LPA and 2 weeks for culture based method). Though the development of assays has been for rifampicin resistance, we need rapid assays for the diagnosis of INH resistance as well to provide appropriate treatment regimen for the patients. RNTCP has recommended a different treatment regimen for INH resistant TB which include three to six months of treatment with injectable second-line drugs with levofloxacin, rifampicin, ethambutol and pyrazinamide followed by continuation phase of six months after stopping injectable agent.[11] If we take IMR to be 10%, there would probably be 2.7 lacs patients with IMR-TB in India. The availability and acceptance of this regimen in such a large number of patients definitely has huge financial implications in national programmes.

Recently, WHO released its recommendations in 2018 and suggested that six months therapy with rifampicin, ethambutol, pyrazinamide and levofloxacin (with or without isoniazid) is recommended to treat IMR-TB.[12] It also suggests to exclude fluoroquinolone resistance prior to initiating the therapy. The guidelines recommended against the addition of streptomycin to conventional regimen to treat IMR-TB. These guidelines have come in the light of a recently conducted meta-analysis which has shown the similar results.[13]

It is essential for all the physicians treating TB to understand the importance of IMR in the management. We, in India, need to strengthen the facilities to identify this neglected entity. The number of patients with IMR-TB is huge and if not managed appropriately, would lead to high rates of MDR-TB cases and poor control of TB. In our opinion, given the large number of patients with IMR-TB and adverse effects of second-line injectable drugs, it is most logical to have an alternative safe regimen for its treatment. WHO recommended regimen of fluoroquinolone, rifampicin, ethambutol and pyrazinamide seems an appropriate choice which is easy to implement to treat IMR-TB. The issue of fluoroquinolone resistance should be taken into account while implementing this strategy under national programmes to control and eradicate TB from India.

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