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Journal Scan

Shorter regimens in treatment of latent tuberculosis—is it effective?

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1. Article information

Four Months of Rifampin or Nine Months of Isoniazid for Latent Tuberculosis in Adults. Menzies D, Adjobimey M, Ruslami R et al. N Engl J Med. 2018; 379:440–453.

2. Background

Traditionally, tuberculosis (TB) control included treatment of only disease cases especially in low-income countries. This strategy was opted because of the high incidence of TB infection even in normal asymptomatic population and treating all of them would be impractical and takes up a huge share of the available resources. The next step in TB control is to treat the latent tuberculosis infection (LTBI). *Mycobacterium tuberculosis* infection is contained initially by host immunity (in most humans). Infection remains in a prolonged, suppressed state termed LTBI. However, latent infection has the potential to develop into active infection at any point of time. Reactivation is seen in immunosuppressed patients, post-organ transplant patients, and patients on anti-tumor necrosis factor alpha therapy.[1]

Before starting treatment for LTBI, all patients must be evaluated for active TB disease to avoid monotherapy and the risk of emergence TB drug resistance.[2] Various regimens were available for treatment of LTBI. The World Health Organization (WHO) recommends isoniazid (INH) daily for six to nine months. Other alternative regimens include rifampicin (RIF) monotherapy (administered daily for four months, WHO recommendation in only low-incidence countries), INH and RIF (administered daily for three months), and INH and rifapentine administered weekly for three months.[3]

3. Summary

Menzies et al. conducted a randomized control trial (RCT) comparing a 4-month regimen of rifampin with a 9-month regimen of INH for the treatment of LTBI in adults. They included 6063 adult patients with LTBI (18 years of age and older) in nine countries and 5744 study participants completed 28 months of follow-up. Their findings include rate of adherence to treatment, and completion was higher with rifampin than with INH therapy (difference, 15.1% points; 95% confidence interval [CI], 12.7 to 17.4, p value < 0.001); the incidence of active TB (clinically or microbiologically confirmed) among the study participants in both the during follow-up was similar (0.10 cases per 100 person-years for rifampin vs. 0.11 cases per 100 person-years for INH), and the incidence of grade 3 to 5 adverse events causing discontinuation of rifampin was significantly lower than that of INH (rate difference, −1.1% points; 95% CI, −1.9 to −0.4).

Regarding the presence of drug resistance among the participants with confirmed active TB (n = 8) in the follow-up, drug-susceptibility test results were not available for four cases (three cases were diagnosed on the basis of histopathology showing necrotizing granulomas, and mycobacterial cultures were contaminated in the fourth sample), two had susceptibility to all drugs tested, and isolates obtained from two participants showed drug resistance. One participant was diagnosed to have RIF-resistant TB in less than two months after completion of the four-month RIF regimen. This was based on the cartridge-based nucleic acid amplification test on the isolate which showed RIF resistance, but phenotypic resistance testing showed susceptibility to all the drugs. Another participant was diagnosed with INH-resistant TB two months after starting INH. These two participants were close contacts of patients with active TB, but drug susceptibility testing for the index cases were not available.

4. Commentary

This study adds to the current literature that indicates that 4-month regimen of rifampin has a clear and statistically significant benefit over the INH monotherapy for LTBI in terms of adherence to treatment. Incidence of hepatotoxicity-related adverse events was also low with RIF regimen than with INH regimen. The findings of this RCT also corroborate evidence from previous trials and observational studies that RIF-based treatment regimens are associated with significantly lower incidence of hepatotoxicity. The trial sites

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for this study varied widely in terms of availability of resources which in turn helps in widespread applicability of results.

Twenty-five percent of global burden of TB is borne by India, and forty percent of our population is infected with TB. The end TB strategy of the WHO was implemented by the Government of India which was emphasized in the National Strategic Plan for elimination of TB 2017–2025. This plan emphasizes on a focussed approach to treat LTBI which includes treating all high-risk patients such as those receiving long-term corticosteroids and immunosuppressants and HIV-infected and juvenile contacts of sputum-positive index cases with a 6-month regimen of INH or shorter 3- to 4-month regimen of INH plus RIF. Irrespective of the regimen used to treat LTBI, ensuring adherence to treatment plays a major role and shorter regimens clearly trumps over longer regimens regarding this issue.

Conflict of Interest

None.

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