A better approach to preventing active TB?

Nine months of isoniazid prevents active TB in those with latent disease. But is there a shorter, less toxic option?

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PRACTICE CHANGER

Use 4 months of rifampin instead of 9 months of isoniazid to treat adults with latent tuberculosis; rifampin is associated with fewer adverse events and higher completion rates.[1]

STRENGTH OF RECOMMENDATION

A: Based on a randomized controlled trial and a previous Cochrane review.

Menzies D, Adjobimey M, Ruslami R, et al. Four months of rifampin or nine months of isoniazid for latent tuberculosis in adults. *N Engl J Med*. 2018;379:440-453.

ILLUSTRATIVE CASE

A 27-year-old daycare worker was tested for tuberculosis (TB) as part of a recent work physical. She presents to your office for follow-up for her positive purified protein derivative (PPD) skin test. You confirm the result with a quantiferon gold test and ensure she does not have active TB. What medication should you prescribe to treat her latent TB infection (LTBI)?

In 2017, there were 9093 cases of new active TB in the United States.[2] It's estimated that one-fourth of the world's population has latent TB.[3] Identifying and treating latent TB infection is vital to achieving TB's elimination.[4,5]

Primary care clinicians are at the forefront of screening high-risk populations for TB. Once identified, treating LTBI can be challenging for providers and patients. Treatment guidelines recommend 4 to 9 months of daily isoniazid.[5-8] Shorter treatment regimens were recommended previously; they tended to be rigorous, to involve multiple drugs, and to require high adherence rates. As such, they included directly observed therapy, which prevented widespread adoption.

Consequently, the mainstay for treating LTBI has been 9 months of daily isoniazid. However, isoniazid use is limited by hepatoxicity and by suboptimal treatment completion rates. A 2018 retrospective analysis of patients treated for LTBI reported a completion rate of only 49% for 9 months of isoniazid.[9] Additionally, a Cochrane review last updated in 2013 suggests that shorter courses of rifampin are similar in efficacy to isoniazid (although with a wide confidence interval [CI]), and likely have higher adherence rates.[10]

STUDY SUMMARY

Rifampin is as effective as isoniazid with fewer adverse effects

The study by Menzies et al[1] was a multisite, 9-country, open-label, randomized controlled trial (RCT) that compared 4 months of daily rifampin to 9 months of daily isoniazid for the treatment of LTBI in adults. Participants were eligible if they had a positive tuberculin skin test or interferon-gamma-release assay, were ≥ 18 years of age, had an increased risk for reactivation of active TB, and if their health care provider had recommended treatment with isoniazid. Exclusion criteria included current pregnancy or plans to become pregnant, exposure to a patient with TB whose isolates were resistant to either trial drug, an allergy to either of the trial drugs, use of a medication with seri-

ous potential interactions with the trial drugs, or current active TB.

Method, outcomes, patient characteristics. Patients received either isoniazid 5 mg/kg body weight (maximum dose 300 mg) daily for 9 months or rifampin 10 mg/kg (maximum dose 600 mg) daily for 4 months and were followed for 28 months. Patients in the isoniazid group also received pyridoxine (vitamin B_6) if they were at risk for neuropathy. The primary outcome was the rate of active TB. Secondary outcomes included adverse events, medication regimen completion rate, and drug resistance, among others.

A total of 2989 patients were treated with isoniazid; 3023 patients were treated with rifampin. The mean age of the participants was 38.4 years, 41% of the population was male, and 71% of the groups had confirmed active TB in close contacts.

Results. Overall, rates of active TB were low with 9 cases in the isoniazid group and 8 in the rifampin group. In the intention-to-treat analysis, the rate difference for confirmed active TB was < 0.01 cases per 100 person-years (95% CI; –0.14 to 0.16). This met the prespecified noninferiority endpoint, but did not show superiority. A total of 79% of patients treated with rifampin vs 63% treated with isoniazid completed their respective medication courses (difference of 15.1 percentage points; 95% CI, 12.7-17.4; $P < .001$). Compared with patients in the isoniazid group, those taking rifampin had fewer adverse events, leading to discontinuation (5.6% vs 2.8%).

This study found that a shorter rifampin-based regimen is associated with improved adherence and fewer adverse events than a longer isoniazid-based regimen for the treatment of latent TB infection.

WHAT'S NEW?

First high-quality study to show that less is more

This is the first large, high-quality study to show that a shorter (4 month) rifampin-based regimen is not inferior to a longer (9 months) isoniazid-based regimen for the treatment of LTBI, and that rifampin is associated with improved adherence and fewer adverse events.

CAVEATS

Low rate of active TB infection and potential bias

The current study had lower-than-anticipated rates of active TB infection, which made the study's conclusions less compelling. This may have been because of a small number of patients with human immunodeficiency virus enrolled in the study and/or that even participants who discontinued treatment received a median of 3 months of partial treatment.

In addition, the study was an open-label RCT, subjecting it to potential bias. However, the diagnosis of active TB and attribution of adverse events were made by an independent, blinded review panel.

CHALLENGES TO IMPLEMENTATION

No challenges to speak of

We see no challenges to implementing this recommendation. **JFP**

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References

1. Menzies D, Adjobimey M, Ruslami R, et al. Four months of rifampin or nine months of isoniazid for latent tuberculosis in adults. *N Engl J Med*. 2018;379:440-453.
2. Stewart RJ, Tsang CA, Pratt RH, et al. Tuberculosis — United States, 2017. *MMWR Morb Mortal Wkly Rep*. 2018;67:317-323.
3. Houben RM, Dodd PJ. The global burden of latent tuberculosis infection: a re-estimation using mathematical modeling. *PLoS Med*. 2016;13:e1002152.
4. Lönnroth K, Migliori GB, Abubakar I, et al. Towards tuberculosis elimination: an action framework for low-incidence countries. *Eur Respir J*. 2015;45:928-952.
5. Uplekar M, Weil D, Lonnroth K, et al. WHO's new end TB strategy. *Lancet*. 2015;385:1799-1801.
6. Centers for Disease Control and Prevention. Treatment regimens for latent TB infection (LTBI). Last reviewed April 5, 2016. https://www.cdc.gov/tb/topic/treatment/ltbi.htm. Accessed January 15, 2020.
7. World Health Organization. Latent TB infection: updated and consolidated guidelines for programmatic management. 2018. Publication no. WHO/CDS/TB/2018.4. https://www.who.int/tb/publications/2018/latent-tuberculosis-infection/en/. Accessed January 15, 2020.
8. Borisov AS, Bamrah Morris S, Njie GJ, et al. Update of recommendations for use of once-weekly isoniazid-rifapentine regimen to treat latent *Mycobacterium tuberculosis* infection. *MMWR Morb Mortal Wkly Rep*. 2018;67:723-726.
9. Macaraig MM, Jalees M, Lam C, et al. Improved treatment completion with shorter treatment regimens for latent tuberculous infection. *Int J Tuber Lung Dis*. 2018;22:1344-1349.
10. Sharma SK, Sharma A, Kadhiravan T, et al. Rifamycins (rifampicin, rifabutin and rifapentine) compared to isoniazid for preventing tuberculosis in HIV-negative people at risk of active TB. *Cochrane Database Syst Rev*. 2013;(7):CD007545.