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Commentary on Evidence Summaries

Rifamycin drugs as alternatives to standard isoniazid treatment to prevent active tuberculosis (TB) in HIV-negative people at risk of developing active TB

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ABSTRACT

In preventing active TB in patients with LTBI with shorter durations of treatment all the regimens included in this review seem to achieve this goal. Most were from the developed countries. In developing countries with high risk of reinfection, the duration of protection offered by a single course of chemoprophylaxis is unknown. In settings where exclusion of active TB can be problematic, TB chemoprophylaxis (especially with rifampicin-containing regimens) needs to be used with great caution.

Research is urgently required into understanding the pathogenesis of latent TB disease, biomarkers to predict progression, improved diagnostics for LTBI and effective treatment regimens for latent infection with drug resistant TB. Cost-effectiveness and implementation research will be required to determine the best strategies to scale-up LTBI treatment at a population level.

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1. The importance of this Cochrane review for global and national tuberculosis control strategies

The prevention of active tuberculosis (TB) in those with latent TB infection (LTBI), or those at high risk of developing TB, is an important component of TB control. Modelling has shown that diagnosis and treatment of LTBI could play a key role in TB

elimination.¹ The World Health Organization (WHO) has recently published guidelines on TB contact investigation and on systematic screening of active TB, both of which offer an entry point to identification of risk groups for LTBI diagnosis and treatment.^{2,3} While LTBI treatment is currently recommended only for a few high-risk groups, a safe, well tolerated and efficacious regimen would help extend this to the wider population, thus paving the way towards true TB “elimination”.

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Isoniazid preventive therapy (IPT) is the mainstay of the WHO recommendations for treatment of LTBI. Apart from concerns of hepatotoxicity the major drawback of isoniazid monotherapy is the long duration of treatment. Poor treatment adherence in persons who have no symptoms is a natural consequence. A regimen of shorter duration is therefore desirable.

This Cochrane systematic review summarizes the evidence from 10 randomized clinical trials that studied four interventions comprising of rifampicin alone or rifamycin in combination with other drugs for two to four months against the standard isoniazid monotherapy of six or nine months in 10,717 predominantly HIV-negative participants.^{4,5}

All four interventions studied, viz., rifampicin monotherapy for three or four months, rifampicin plus isoniazid for three months, rifampicin plus pyrazinamide for two months and rifapentine plus isoniazid once a week by DOT for three months, were not different from isoniazid given alone for six or nine months in terms of preventing active TB. Adherence to treatment was significantly better in the shorter rifampicin monotherapy regimen and the weekly rifapentine–INH combination regimens. Hepatotoxicity was higher in the rifampicin plus pyrazinamide regimen, but lower in the rifampicin monotherapy and rifapentine plus isoniazid weekly regimen compared to isoniazid monotherapy.

2. Challenges and unanswered questions

In terms of the primary objective of shortening the duration of treatment all the regimens included in this review seem to achieve this goal, though the strength of the evidence leaves much to be desired. Most of the trials included in this review are from the developed countries. It is a moot point whether these results would be generalizable to the developing countries which bear the major TB burden. Apart from the high risk of reinfection, the duration of protection offered by a single course of chemoprophylaxis is unknown. While TB preventive therapy should be prioritized in high-risk groups, the feasibility of implementing it in a wider context needs careful consideration. In settings where exclusion of active TB can be problematic, TB chemoprophylaxis (especially with rifampicin-containing regimens) needs to be used with great caution.

The basic biology of *Mycobacterium tuberculosis* latency is not well understood and we do not have reliable biomarkers to predict which individuals with LTBI will progress to active disease (likely in only 5%–20%). Research is urgently required into understanding the pathogenesis of latent TB disease, biomarkers to predict progression, improved diagnostics for

LTBI and effective treatment regimens for latent infection with drug resistant TB. Before initiating LTBI treatment, it is essential that active TB is effectively ruled out and the diagnosis of LTBI reliably established. The tuberculin skin test (TST) and interferon-gamma release assays (IGRA) are designed to detect cellular immune response to *M. tuberculosis*, but do not differentiate between latent infection and active disease and, if negative, do not allow TB infection to be ruled out.

Several ongoing clinical trials are testing the efficacy of shorter and/or intermittent regimens to treat LTBI, and of supervised versus self-administered treatment. These trials should provide more data to inform health policy decisions.

3. Conclusion

For LTBI treatment to become a reality in high TB burden countries, in addition to answering these basic scientific questions, cost-effectiveness and implementation research will be required to determine the best strategies to scale-up LTBI treatment at a population level.

Conflicts of interest

All authors have none to declare.

REFERENCES

1. World Health Organization. *Global TB Report 2013*. Geneva: World Health Organization; 2013.
2. World Health Organization. *Recommendations for Investigating Contacts of Persons with Infectious Tuberculosis in Low- and Middle-Income Countries*. Available at: http://apps.who.int/iris/bitstream/10665/77741/1/9789241504492_eng.pdf.
3. World Health Organization. *Systematic Screening for Active Tuberculosis – Principles and Recommendations*. Available at: http://apps.who.int/iris/bitstream/10665/84971/1/9789241548601_eng.pdf.
4. Sudarsanam TD, Tharyan P. Rifampicin mono-therapy or rifamycin-combination therapy compared to isoniazid monotherapy for preventing active TB in HIV-negative people at risk of developing active TB: summary of the evidence and implications for public health programmes. *Clin Epidemiol Glob Health*. 2014;2(1):28–36.
5. Sharma SK, Sharma A, Kadiravan T, Tharyan P. 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 Jul 5;7:CD007545. <http://dx.doi.org/10.1002/14651858.CD007545.pub2>.