Intermittent Short Course Rifapentine-Isoniazid Combination for Preventing Tuberculosis in Children

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SUMMARY

In this randomized, open-label clinical trial conducted at 29 sites across 5 countries, 1058 children (aged 2-17 years), who were eligible for treatment of latent tuberculosis infection, were randomized to receive either 12 supervised once-weekly doses of the combination drugs (rifapentine and isoniazid) for 3 months, or 270 daily doses of isoniazid, without supervision by a health care professional, for 9 months. Of the 471 in the combination-therapy group, 415 (88.1%) completed treatment *vs* 351 of 434 (80.9%) in the isoniazid-only group (P =0.003). The 95% CI for the difference in rates of discontinuation attributed to an adverse event was within the equivalence range. Three of 539 participants (0.6%) who took the combination drugs had grade 3 adverse events (AE) as against 1 of 493 (0.2%) who received isoniazid only. Neither arm had any hepatotoxicity, grade 4 adverse events, or treatment-attributed death. None of the 471 in the combination-therapy group developed tuberculosis as against 3 of 434 (cumulative rate, 0.74%) in the isoniazid-only group.

COMMENTARIES

Evidence-based Medicine Viewpoint

Relevance: There is ample literature documenting the individual and public health benefits of chemo-prophylaxis for asymptomatic children believed to be at high(er) risk of developing tuberculosis (TB). This includes children living in contact with confirmed tuberculosis cases and/or those with latent TB. The Revised National Tuberculosis Control Program [1,2] and Indian Academy of Pediatrics [3] recommend using isoniazid (10 mg/kg daily) for 6 months, after ruling out active disease in these children. In contrast, the Centers for Disease Control, USA (CDC) previously recommended [4] using isoniazid for 9 months in contacts with latent TB (i.e., presence of infection but not disease). Longer duration of prophylaxis is generally associated with poorer adherence. In addition, isoniazid has the potential to cause unpleasant adverse events including hepatotoxicity. Therefore, alternate regimens with shorter drugs and/or durations are sought for chemo-prophylaxis.

In 2011, the CDC concluded that directly observed weekly administration of isoniazid with rifapentine (INH-RPT) for 12 weeks, has equivalent efficacy and safety compared to the traditional 9 months daily INH regimen. This was based on the results of a well-designed, unblinded, multi-center, non-inferiority RCT in people older than 12 years [5] which reported equivalence of weekly directly observed INH-RPT combination for 12 weeks and daily unsupervised INH for 9 months (standard protocol). The two regimens had similar efficacy for prevention of TB over nearly 3 years follow-up (cumulative rate 0.19% for the combination *vs* 0.43% for monotherapy). However, adherence to the regimen was significantly better with the combination (82% *vs* 69%). Although the group receiving combination regimen had a higher discontinuation rate due to adverse effects (4.9% *vs* 3.7%), hepatotoxicity was much lower (0.4% *vs* 2.7%). Therefore the CDC recommended that the shorter INH-RPT regimen could be used to boost adherence [6].

In contrast, the World Health Organization (WHO) position appears to be more flexible and the 2015 guidelines permit any of five different options *viz* daily INH for 6 or 9 mo, or weekly INH-RPT for 12 weeks, or daily isoniazid-rifampicin combination (INH-RMP) for 3-4 mo, or daily rifampicin for 3-4 months [7]. These variations suggest that the issue needs greater exploration to identify the optimal regimen.

Rifampicin and Rifapentine belong to the rifamycin group of drugs that act against Mycobacteria by

inhibiting bacterial DNA-dependent RNA polymerase [8]. However, rifapentine has a significantly longer elimination half-life than rifampicin (>12 h *vs* 2-3 h). Following oral ingestion, it achieves a plasma concentration much higher than the desired minimum inhibitory concentration (MIC) and serum levels remain higher than the MIC for over 72 hours [9]. Interestingly, consumption with food (especially lipid-rich meal) increases the peak serum concentration, in contrast to rifampicin that needs to be taken in a fasting state. Like other rifamycins, rifapentine also has the potential to cause adverse events, including hepatotoxicity. The establishment of rifapentine pharmacokinetics in children [10] expanded the scope of using the drug in children as well.

Against this backdrop, the recent publication of pediatric data [11] from the INH-RPT versus INH trial described above [5] is a significant new addition to the existing knowledge on the subject of chemoprophylaxis in children. A summary of the trial [11] details is shown in ***Table* I**.

Critical appraisal: Overall, the trial had high risk of bias, based on unclear randomization process, inadequate allocation concealment, absence of blinding, and failure to report data as intention-to-treat. The investigators reported sample size calculation based on efficacy outcome in the adult trial [5]. However for this trial [11], they simply extrapolated these calculations. This may account for recruitment of nearly twice the number of children specified in the sample size calculation.

The trial was conducted over 13 years (10 years of recruitment and nearly 3 years of follow-up). The investigators did not report whether there were significant changes in TB prevalence rate, control strategies and definition during this period.

It is interesting that despite supervised (directly observed) weekly regimen, only 88% children completed INH-RPT therapy, while 81% children completed 9 mo unsupervised therapy with INH. This has two implications. First, almost 1 in 8 children failed to complete treatment despite the best possible supervision/monitoring in a research setting. This suggests that the treatment completion rate is likely to be lower in the real world setting. Second, the difference from the unsupervised group was only 7%. This is a very high completion rate in the unsupervised group, given that only 69% in the adult trial [5] completed this arm of therapy. This has programmatic implications also since supervised/observed treatment is expected to result in better treatment completion rates.

A 2013 Cochrane review [12], incorporating data from the previous trial [5], reported equivalent success rate with either regimen (RR 1.04, 95% CI 0.18, 1.07). However, INH-RPT combination resulted in better adherence (RR 1.19, 95% CI 1.16, 1.22), less serious adverse events (RR 0.55, 95% CI 0.40, 0.74) and lower hepato-toxocity (RR 0.16, 95% CI 0.1, 0.27). However, the occurrence of adverse events resulting in discontinuation of treatment was more frequent with the combination (RR 1.32, 95% CI 1.07. 1.64). A more recent systematic review incorporating a network meta-analysis [13] designed to identify the most efficacious strategy for preventing TB reported equivalent success (compared to the standard INH monotherapy) with 3 mo INH-RMP combination, 3-4 mo rifampicin alone, and INH-RPT used in this trial [11]. However it should be noted that many of the comparisons in a network meta-analysis are indirect estimates rather than direct (head-to-head) comparisons.

The cost-benefit ratio of higher expense for monitoring *versus* lower expense for reduced number of doses of medication (albeit more expensive per dose) needs to be calculated. The authors [11] did not discuss the cost implications of increased monitoring for adverse events that may be required for the INH-RPT combination or the implications of switching therapy should such a need arise. The current CDC guideline [6] correctly points out that choosing between INH monotherapy *versus* INH-RPT combination ought to be influenced of programmatic considerations related to direct observation, availability of drugs, and resources to manage adverse events.

Extendibility: There are many similarities between the children in the trial [11] and Indian children in the general population. Over 90% were recruited because of close contact with a confirmed case of TB, rather than other high-risk categories. Although the cut-off for a positive tuberculin skin test was 5 mm, majority of children had induration greater than 10 mm (which is the cut-off used in India). The overall HIV prevalence was 2.3%; although this is significantly higher than the population average in India, it is reasonable in terms of TB prevalence. About 3.2% enrolled children were in contact with cases resistant to isoniazid or rifampicin, which is similar to the global average. However, the trial [11] did not include infants below 2 y, and those with weight <10 kg; these two groups form an important subgroup of children who receive chemoprophylaxis in India.

There are no therapy or prophylaxis trials with rifapentine in India. An older systematic review [14]

TABLE I SUMMARY OF THE TRIAL

Objective	To compare the efficacy and safety of weekly directly observed INH-RPT combination for 12 weeks versus daily unsupervised INH for 9 months, in children (2-17y) with latent TB.
Study design	Multi-centre, unblinded, parallel group, non-inferiority, randomized controlled trial.
Study setting	29 centers in 5 countries (USA, Canada, Spain, Brazil, Hong Kong)
Study duration	Recruitment during 2000-2010
Population (P)	*Inclusion criteria:* Children (initially 12-18 y and later 2-11 y) deemed to be at high(er) risk of developing TB disease based on living in contact with a culture-confirmed case of tuberculosis, positive Tuberculin skin test, and history of exposure to TB. The authors did not clearly define the criteria used for these three groups. *Exclusion criteria:* TB disease (suspected or confirmed), confirmed resistance to INH or rifamycin in the index case, prior treatment with either drug, known intolerance to rifamycin, transaminitis, pregnancy/ lactation, or weight <10 kg.
Intervention (I)	Weekly administration of INH-RPT combination over 12 weeks under direct observation. The regimen was deemed complete if at least 11 doses were taken during a period of 10-16 weeks. Dosage of rifapentine was as per weight viz 300 mg for 10-14 kg, 450 mg for 14-25 kg, 600 mg for 25-32 kg, and 750 mg for 32-50 kg.
Comparison (C)	Daily INH for 270 days, but not necessarily supervised. Adherence was calculated by interviewing the child/parent and counting left over pills. The regimen was deemed complete if at least 240 doses were taken during a period of 35-52 weeks
Outcomes (O)	*Efficacy:* TB cases (detected by active search) defined as culture-confirmed or clinical diagnosis as per criteria set by CDC and American Thoracic Society. Adherence measured as treatment discontinuation on account of adverse events. *Safety:* Adverse events recorded by investigators from start if therapy till 60 days after the last dose. Serious adverse events defined as mortality within 60 days of last treatment dose, hospitalization, life-threatening event or disability.
Time-frame (T)	*Follow-up protocol*: 3 mo, 6 mo, 9 mo, 12 mo, 15 mo, 18 mo, 21 mo, 27 mo and 33 mo after last dose or discontinuation of treatment.
Sample size	*A priori* sample size calculation required 644 children to generate 80% power to confirm non-inferiority between the two intervention arms in terms of rate of therapy discontinuation due to adverse events. However, a total of 1058 were enrolled.
Similarity of groups at baseline	The two groups were comparable with respect to ethnicity, criteria for latent TB, HIV sero-status, TST reaction size, and BMI. However there were more boys in the INH-RPT group.
Randomization	Process not explicitly defined
Allocation concealment	Not mentioned
Blinding	Participants, investigators or outcome assessors were not blinded.
Selective outcome reporting	All relevant outcomes were reported.
Incomplete outcome reporting	Efficacy outcomes were reported in 471/552 (85%) and 434/506 (86%) enrolled children in the intervention and comparison groups respectively. These data were reported as a modified intention-to-treat analysis.
Main results (INH-RPT *vs* INH alone)	Development of TB: 0/471 *vs* 3/434; RR 0.13, 95% CI 0.01, 2.54
	Treatment completion: 415/471 (88%) *vs* 351/434 (81%); RR 1.09, 95% CI 1.03, 1.15
	Treatment discontinuation due to AE: 8/471 (1.7%) *vs* 2/434 (0.5%), RR 3.69, 95% CI 0.79, 17.26
	SAE attributed to treatment: Nil in either group
	AE attributed to treatment: 11/539 (2%) *vs* 5/493 (1%); RR 2.01, 95% CI 0.70, 5.75
	Severe AE (Grade 3): 3/539 (0.6%) *vs* 1/493 (0.2%), RR 2.74, 95% CI 0.29, 26.29
	Hepatotoxicity: Nil in either group

comparing rifapentine (RPT) containing therapy (administered twice weekly) *vs* rifampicin (RMP) containing combinations (administered daily) identified 9 RCTs, and reported comparable treatment success (cure) rate, relapse rate, adverse event rate, and hepatotoxic effects. However, when rifapentine combinations were used once per week, it resulted in higher relapse rate compared to twice of thrice weekly rifampicin based regimens.

Nevertheless, it seems that the combination used in this trial [11] could be explored for chemoprophylaxis in Indian children also. However, it appears that rifapentine is yet not available in India.

Conclusions: This RCT suggests that rifapentine-based combinations hold promise for chemoprophylaxis in children at risk of developing tuberculosis disease. However, the high risk of bias, limitations with extendibility, and absence of cost-effectiveness analysis spell the need for more research before recommendations for routine practice can be confidently made.

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Infectious Disease Specialist's Viewpoint

India is a high tuberculosis (TB) burden country only because we tolerate TB. Modern medicine does not tolerate infectious diseases – by healing and by preventing. Pediatrics promotes prevention – through immunizations, good nutrition and stimulating cognitive development. When it comes to TB, many are confused about prevention.

Mycobacterium tuberculosis (MTb) infection occurs as micro-outbreaks in households of adults with pulmonary TB, and sporadically for all others. BCG does not prevent infection, but protects against meningitis and military TB in young infected children [1]. But what about other outcomes of infection? For a few years MTb would be in slow multiplication mode before becoming non-multiplying 'latent TB infection' (LTBI). The former is a window of opportunity when MTb can be killed off with 'preventive treatment.'

We identify infected children by Mantoux test with Purified protein derivative (PPD). By age 5, the cross-

reactivity from BCG would have markedly declined – so, that is a good age for routine testing. If positive, infection was recent – the child has lived only 5 years. Isoniazid (INH) alone for 9 months, even 6 months, is the standard preventive treatment. With rifampicin plus INH, the duration can be reduced to 3-4 months [2]. Motivating parents to give drugs daily to complete the course is not easy.

In USA in adolescents and adults rifapentine and INH given once weekly for 12 week is as effective as the longer regimens. This recent publication [3] shows this 12-dose regimen effective even in children below the age of 12 years. As soon as rifapentine gets registered in India, preventive treatment will become quite easy.

There is no excuse for not promoting preventive treatment in high burden countries [4]. If we neglect pediatric MTb infection, we will never be able to control adult TB [4].

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Pediatric Pulmonologist's Viewpoint

The authors describe a non-inferiority randomized controlled trial comparing two regimens for treatment of latent tuberculosis infection (LTBI) in children. The results show that weekly twelve dose observed regimen of isoniazid/rifapentine is non-inferior to the standard regimen of unobserved nine months of isoniazid.

The isoniazid and rifapentine combination regimen has benefits of early completion in 3 months and weekly observed doses which led to better completion rates with equal efficacy (measured by the rate of incidence of tuberculosis in follow up) compared to isoniazid alone. The shorter combination regimen appears to have a similar safety profile as the single drug INH regimen as the risk of hepatotoxicity was not increased in the two drug regimen.

While the treatment of LTBI is an important strategy for control of TB in the affluent low burden countries, the role of LTBI is far more limited in high burden countries as the preventive therapy does not have a lasting benefit and does not cover for any subsequent infection. This limits the use of any preventive therapy only to the young children (under 6 years) who are at a high risk of disseminated disease after infection. At present, there are several issues with usage of Rifapentine in children as there is non-availability of safety and cost-effectiveness data in children less than 2 years and less than 10 kg. Since there are no pediatric formulations, therefore crushed tablets mixed with food are given to children. This adds complexity as the available reports have shown inconsistent bioavailability with such usage. In general, the experts have reservation about using rifamycin-based preventive therapy in our country because of the possible risk of emergence of drug-resistance to this very potent but vulnerable drug.

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