Combination of Isoniazid and Rifampin for the Prevention of Failure of Standard Therapy for Latent Tuberculosis Infection in Children: Evidence Base Case Report

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Abstract

Tuberculosis (TB) control program in children is carried out with three strategies: finding and treating adult TB cases (as a source of transmission), treating latent TB infection, and administering the BCG vaccine. There is a high risk of transmission in children in close contact and living at home with adult patients. After Mycobacterium is inhaled through the respiratory tract, then the body's resistance to Mycobacterium tuberculosis occurs. Furthermore, there are two possibilities: only TB infection occurs, or the child has TB disease. We report one case: a boy, age four years, diagnosed with latent TB infection. This diagnosis is based on the findings of the 13 mm tuberculin test (positive). There is a history of contact with adult TB patients. On physical examination, no abnormalities were found. Likewise, the chest X-ray examination also found no abnormalities. Due to the diagnosis of latent TB infection, prophylaxis with Isoniazid was planned for six months. In the first month, the child still wants to take medication according to the rules. However, entering the second month, children sometimes do not want to take medication. This situation raises concerns about the possibility of therapy failure. His mother was very worried about this condition. Therefore, doctors offer to provide a combination pattern of therapy in isoniazid with rifampicin, with a span of 3 months. Standard therapy with INH alone was discontinued. This therapeutic decision was based on a study that combined INH with rifampin for three months gave better results than single prophylactic therapy with INH.

Keywords: Latent Tuberculosis infection, Isoniazid, Rifampisin, Combination Therapy.

Case Summary

A boy aged four years was brought by his mother for re-control and taking other therapy drugs with a diagnosis of latent tuberculosis infection at the Children's Polyclinic of Zainoel Abidin General
Previously, the child was diagnosed with latent TB infection (LTBI) because he only had a history of contact with his mother, who had pulmonary TB disease. There are no other complaints that support the diagnosis of TB disease. On physical examination, no abnormalities were found. Likewise, the chest X-ray examination was also within normal limits. Positive results were found only in the tuberculin test, where the induration diameter was 13 mm (positive). Because he was diagnosed with LTBI, he was given a standard drug in Isoniazid (INH). In the first month, the child still wants to take medication according to the rules. However, entering the second month, children sometimes do not want to take medication. This situation raises concerns about the possibility of therapy failure. His mother was very worried about this condition. Therefore, doctors offer to provide a combination pattern of therapy in isoniazid (INH) with rifampin (R), with a span of 3 months. Standard therapy with INH alone was discontinued.

**Clinical Problems**

From the summary of the cases above, the child only had a TB infection and had not yet suffered from TB disease. This diagnosis was based on the finding that there was only a history of contact with the mother who had TB disease (smear-positive). Evidence that the child has been infected has a positive tuberculin test result (induration 13 mm). In this case, the child had received standard prophylactic treatment in INH, which was planned for six months. However, the problem is that after one month of therapy, the child begins to show boredom taking medication. This condition raises concerns about the possibility of therapy failure. Therefore, a policy was taken to discontinue standard therapy with INH alone and replace it with a combination pattern: INH and rifampin, with an extended therapy plan for three months. After the therapy is finished, re-examination is done, whether the child is still healthy or has TB disease.

The change in therapy from standard therapy with INH alone to a combination of INH with rifampin is undoubtedly based on scientific studies and evidence-based case reports by analyzing several studies comparing these therapeutic patterns. We will examine the study results regarding the level of adherence of children to standard INH therapy compared to the combination of INH and rifampin. Thus, the change of therapy can be carried out until the end of the optimally planned time. An analysis of the tenacity of this issue can be seen in Table 1.

| Population (P) | Indicator (I) | Control (C) | Outcome Result (O) | Adherence level |
|----------------|--------------|-------------|--------------------|-----------------|
| Children with latent TB infection (LTBI) | Combination of INH and Rifampicin prophylaxis for 3 or 4 months | Prophylaxis with single INH for 6 months | |

**Tracing Methods**

An online literature search procedure was carried out using the Pubmed search instrument, Highwire google, springer link, and Elsevier to address these clinical questions. Keywords used are "isoniazid," "rifampin, latent tuberculosis infection, children, from publications with a span of 15 years. Search results obtained two articles that are considered relevant to the problem. The level of evidence is determined based on a classification issued by the Oxford Center for Evidence-based Medicine of evidence (Philips et al., 2021).

**Results**

A search of the articles in this paper found two articles that were relevant to the clinical question. These two articles are a meta-analysis and a retrospective cohort conducted by Spyridis et al. (2007) and Van Zyl et al. (2006). These two studies aimed to determine the effectiveness of the combination of INH with rifampin compared to standard therapy with INH alone in the treating of latent TB infection in children.
Table 2. Summary of Study

| Parameter | Spyridis et al. 2007 | Van Zyl et al. 2006 |
|-----------|----------------------|----------------------|
| Title     | The effectiveness of 9-month regimen of isoniazid alone versus 3- and 4-month regimens of isoniazid plus rifampin for treatment of latent tuberculosis infection in children. | Adherence to anti-tuberculosis chemoprophylaxis and treatment in children. |
| Aims      | Compared a combination regimen of isoniazid plus rifampin for 3 and 4 months with a regimen of isoniazid monotherapy for 9 months for the treatment of LTBI in children. | Determine adherence to anti-tuberculosis chemoprophylaxis and treatment in children evaluated as household contacts of pulmonary tuberculosis cases with adults. |
| Method/Level of evidence | RCT prospektif/ 1b | Cohort retrospektif/ 2b |
| Result    | P Assessment uses urine strips that can detect metabolic INH and rifampin. A total of 850 of 926 (91.8%) patients had good adherence. The non-adherence rate was higher in group A compared to group B (p = 0.029) while in groups C and D there was no significant difference (p = 0.533). | Adherence to 6H therapy versus 3HR 2/19 (10.5%): 43/66 (65.2%) (p < 0.001; OR 0.06; 95% CI 0.01-0.032). |
| Conclusion | The three-month regimen of INH and rifampin was equivalent to that of 4 months of INH and rifampin, and both regimens were superior to 9 months of INH. Higher adherence rates with shorter regimens are more effective in treating INH-resistant and rifampin-sensitive mycobacterial infections. Drug-related side effects are generally rare in children receiving antituberculosis drug therapy so that shorter-term therapy is equally safe. | A combination of INH and rifampin chemoprophylaxis for three months can be considered to improve adherence to TB chemoprophylaxis, but prospective studies are still needed to compare adherence, costs, and outcomes between INH chemoprophylaxis given for 6-9 months with a combination of INH and rifampin given for three months. Three months in children who have contact with adult cases |

Spyridis et al. conducted a prospective randomized controlled trial (level of evidence 1b) for more than 11 years (1995-2005) on 926 children <15 years who met the criteria for latent TB infection based on the International Union Against Tuberculosis and Lung Disease, American Academy of Pediatrics (AAP), and British Thoracic Society (BTS). There are four groups in this study. Group A (n = 232) received nine months of INH therapy, group B (n = 238) received four months of INH and rifampicin therapy, group C (n = 232) received four months of INH and rifampicin therapy, and group D (n = 220) received three months of INH and Rifampicin therapy. Overall, as many as 850 of 926 (91.8%) patients had good medication adherence. The non-adherence rate was higher in group A than in B (p = 0.011). Meanwhile, there was no significant difference in groups C and D (p = 0.533) (Spyridis et al., 2007).

Patients with a high or moderate level of adherence, on radiological examination, detected the presence of active disease such as hilar adenopathy and/or lesions of the lung parenchyma after four months of therapy, found 48 of 200 (24%) patients in group A. 220 (11.8%) children in group B (p = 0.001). New radiological findings were found in 30 of 221 (13.6%) of
group C, and 23 of 209 (11%) patients of group D (p = 0.418). It can be concluded that the administration of the INH regimen and rifampin for three months has efficacy equivalent to that of the administration of INH and rifampin for four months, and both regimens are superior to the administration of INH for nine months. The adherence rate is higher with a shorter regimen, more effective in treating INH-resistant and rifampin-sensitive mycobacteria infections (Spyridis 2007).

Van Zyl et al. (2006) conducted a retrospective cohort study (level of evidence 2b) of 335 children under five years of age with known household contacts with 243 cases of adult pulmonary TB from January 1996 to September 2003. A total of 99 (27.4%) children were diagnosed with TB disease, 93 (25.8%) were diagnosed with TB infection (LTBI), and 134 (37.1%) were diagnosed with TB exposure. Adherence to taking antituberculosis drugs was 82.6%, significantly better than 44.2% adherence to TB chemoprophylaxis (p <0.001; odds ratio (OR) 6.83; confidence interval (CI) 95% (3.6-2.96) Adherence to chemoprophylaxis combination INH rifampicin given for 3 months 69.6% was significantly better than 27.6% adherence to INH chemoprophylaxis alone given for 6 months (p <0.001; OR 4.9; CI 95% 2.4-10.36). In this study, it can be concluded that the administration of chemoprophylaxis in combination with INH and rifampin for three months can be considered to improve adherence to TB chemoprophylaxis. However, it is still necessary to conduct a prospective study comparing adherence, costs, and outcomes between INH chemoprophylaxis given for 6-9 months with a combination of INH and rifampin given for three months in children who have contact with adult cases (Van Zyl 2006).

Discussion

Latent tuberculosis infection (LTBI) is a state of persistent immune response to Mycobacterium tuberculosis antigen without evidence and clinical manifestations of active tuberculosis. Therapy of LTBI with INH will reduce the incidence of developing active TB infection and reduce the number of adults who will infect other people. Administration of INH chemoprophylaxis for 3 and 6 decreased the risk of TB by 21%, 65%. Administration of INH for nine months can have an optimal protective effect, so this regimen is generally recommended by the American Academic of Pediatrics (AAP) for children and adolescents (Ichikawa et al., 2017, Villarino et al. 2015, Thomas 2017).

Therapy with INH for 6-9 months has long been used as the standard therapy pattern in treating latent TB infection. The effectiveness of INH in clinical practice is lower than the efficacy shown in clinical trials because the adherence to completing INH therapy for up to 9 months is less than 50%. There are several alternative therapeutic regimens for latent TB infection, including rifampicin alone for four months, a combination of INH and rifampin for three months, and a combination of pyrazinamide and rifampicin for two months. The administration of pyrazinamide and rifampicin for two months was associated with severe liver injury and death. The British Thoracic Society (BTS) in 1998 recommended the administration of a combination of INH and rifampin for three months as an alternative therapy for latent TB infection, with a shorter administration time, although these recommendations are based on limited information (Joint, 2000; Villarino et al., 2015).

The study conducted by Spyridis et al. concluded that the administration of the INH and rifampicin regimens for three months had an efficacy equivalent to the administration of INH and rifampin for four months, and both regimens were superior to that of administering INH for nine months. The adherence rate is higher with a shorter regimen, more effective in treating INH-resistant and rifampicin-sensitive mycobacteria infections (Spyrandis et al., 2007). This is similar to the cohort study conducted by Van Zyl et al., eight, which concluded that the combined chemoprophylaxis of INH and rifampicin for three months could be considered to improve adherence to TB chemoprophylaxis (Van Zyl 2006).
The choice of a treatment regimen must balance the efficacy (degree of protection shown in clinical trials) and the incidence of side effects (relatively low in children in all regimens), adherence, and drug sensitivity to isolates obtained from TB patients who have contact with the child (Martinez et al., 2017). High efficacy regimens will be of limited effectiveness if the patient does not complete therapy completely. A study by Vallario et al. (2015) of 15 children aged 2-17 years showed that the 3HP regimen was as safe and effective as the 9-month isoniazid regimen. ILTB treatment with the 3HP regimen had a higher adherence rate than the 9-month isoniazid regimen (88.1% VS 80.9%; 95% CI; p = 0.003). These studies recommend the use of the 3HP regimen in children with ILTB aged 2-17 years. Currently, there are no safety and pharmacokinetic data in children aged <2 years. To date, this regimen is not yet available in Indonesia. The limited availability of rifampicin means that the use of this regimen is not yet widespread (Cruzz et al., 2013, Ichikawa 2017).

In this case, study, which is discussed here, the patient was a four-year-old boy diagnosed with latent TB infection (LTBI). The patient received INH prophylaxis for six months. From the history, it was found that there were contacts with adult TB patients. Based on research conducted by Nurwitasari et al. (2015), factors associated with the incidence of tuberculosis in children include contact history, nutritional status, length of contact, and closeness to contact.

Meanwhile, according to research conducted by Diani et al. (2011), are risk factors for exposure to tuberculosis are the number of sources of transmission, sputum AFB, and population density/occupancy (Nurwitasari et al. 2015, Diani et al., 2011). At the same time, other risk factors for infection are air circulation/ventilation and exposure to cigarette smoke. Several studies stated that children who live in the same house with adult pulmonary TB sufferers are at high risk for TB infection and illness. Tracing of household contacts (Contact Screening) can to reduce TB morbidity and mortality in children (Diani et al., 2011, Martinez et al., 2017).

From the discussion above, the policy to discontinue standard therapy (INH only) and replace it with a combination of INH with rifampin seems to be providing optimal therapeutic success. This is mainly based on a study conducted by Spyridis et al. (2006) which concluded that the administration of the INH regimen and rifampicin for three months has the same efficacy as the therapy for INH and rifampin for four months. Both regimens were also superior to the nine months of INH alone. Likewise, a study conducted by Van Zyl et al. (2006) concluded that the administration of INH and rifampin for three months could be considered to improve adherence to TB chemoprophylaxis. In this case, there is a risk of therapy failure if only the INH therapy pattern is used for six months. Long therapy time will cause boredom. Therefore, the combination pattern of INH and rifampin, which is only three months, seems more likely to guarantee optimal therapy success (Van Zyl et al., 2006, Villarino et al., 2015).

**Conclusion**

We have reported one case of latent tuberculosis infection (LTBI) in children who had received therapy with the INH therapy pattern only. After one month of therapy, the child exhibited difficulty taking medication, so there was a concern that therapy failure would occur. Therefore, changing the therapy pattern with the combination of INH with rifampicin for three months will better guarantee the success of therapy because of the short therapy period. Based on evidence-based case studies, from several scientific studies that have been presented, it can be concluded that the prophylactic treatment of INH and rifampicin for 3 or 4 months has the advantage of a higher level of adherence than standard INH therapy for six months. Thus, one conclusion based on evidence (evidence-based) that is strong enough to apply to similar clinical problems later, regarding the use of INH and rifampicin therapy patterns for three months to prevent treatment failure of other TB infections in...
children, mainly because of boredom in taking medication. There is a need for further prospective studies comparing adherence to cost between the INH prophylaxis given six months with the combination of INH and rifampin given for three months in children who have contact with TB cases in adults.

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