Title: Adverse events associated with weekly short course isoniazid and rifapentine therapy in pediatric patients with latent tuberculosis: a chart and literature review

Key Words: 3HP, directly observed therapy, antitubercular agents, drug therapy, therapy

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Summary/Abstract

Background: Effective yet safe treatment of latent tuberculosis is important for preventing the spread of tuberculosis and the progression to active disease in pediatric patients. As of 2017, the short course combination regimen of weekly isoniazid and rifapentine (3HP) administered by directly observed therapy (DOT) has replaced 9 months of isoniazid as the standard of treatment for latent tuberculosis in pediatric patients. The literature, limited in size, has established the 3HP regimen's superior safety and adherence.

Methods: We completed a retrospective chart review (n = 22) of pediatric patients at our institution receiving this regimen between 2017 and 2019. Frequencies of selected outcomes were compared to data collected in a literature review.

Results: In this retrospective chart review, pediatric patients ages 2 to 20 years receiving 3HP with DOT for latent tuberculosis experienced higher adverse event rates, more severe adverse events, and higher treatment discontinuation than that which has been previously reported in the literature. A possible explanation for this finding is that our cohort's race/ethnicity differed from the cohorts used in the literature.

Conclusions: Our data suggests that the short course combination regimen for pediatric latent tuberculosis patients may have a higher adverse event rate than previously established. Although this sample size is small, this study urges further investigation of more diverse cohorts to better establish the regimen's safety and tolerability.

Introduction

The global burden of latent tuberculosis infection (LTBI) is 1.8 billion, or approximately 23% of the world's population.[1] In the United States, 4.7% of the population is estimated to have latent tuberculosis.[2] Safe and effective treatment for latent tuberculosis in children provides a substantial public health benefit by preventing progression to active tuberculosis disease.[3]

In 2011, the CDC first recommended the short-course combination regimen of weekly isoniazid and rifapentine for 12 weeks (3HP) administered by directly observed therapy (DOT) for patients 12 years and older based on the results of the PREVENT TB trial.[4] The PREVENT TB trial showed that the 3HP regimen offers advantages such as a shorter course of therapy and higher completion rate when compared to the 9 month daily isoniazid (9H) therapy.[5] These studies concluded that 3HP therapy for latent tuberculosis was as safe and effective as 9 months of isoniazid in preventing development of tuberculosis. However in 2011, there was not enough clinical evidence to make a recommendation for the 3HP regimen in children less than the age of 12.[4]

In 2017, the CDC revised their recommendation to include pediatric patients ages 2 to 11 years old.[6] This recommendation was made on the basis of results published in a single, large randomized controlled trial completed by Villarino et al that concluded that the 3HP regimen administered by DOT was as safe and more effective than the 9H regimen, while also improving treatment completion rates in pediatric populations. This trial was an extension of the PREVENT TB Trial.[3] Cruz and Stark completed two retrospective cohort studies following the publication of Villarino et al's article.[7,8] These two studies found that the 3HP treatment had higher treatment completion rates and demonstrated fewer side effects than the 9H regimen for patients less than

18 years of age.[7,8] In 2017, our institution implemented 3HP with DOT for latent tuberculosis, and we evaluated the adverse event rate in our patient population..

Materials and Methods

Data obtained from a retrospective medical chart review of pediatric patients treated for latent tuberculosis with the 3HP regimen with DOT at Cincinnati Children's Hospital Medical Center (CCHMC) was analyzed in order to identify clinical and demographic factors associated with adverse events. First, a literature review was completed in order to investigate adverse event rates associated with 3HP therapy administered by DOT for latent tuberculosis in pediatric patients. The articles were obtained using relevant search terms in PubMed. Relevant search terms included 'short course combination isoniazid and rifapentine', '3HP', 'directly observed therapy', 'pediatric', 'children', and 'latent tuberculosis'. Three articles obtained from the literature review both observed and reported 3HP adverse event rates and treatment adherence in pediatric populations with a latent tuberculosis diagnosis. Articles that included pediatric patients in a cohort containing both children and adults, but did not report data specifically for pediatric patients, were excluded from the literature review.

Medical records were abstracted from latent tuberculosis patients less than 20 years of age who were treated with the 3HP regimen with DOT between January 2017 and June 2019 in the Infectious Diseases Clinic and International Adoption Center at CCHMC. DOT was defined as supervision of weekly doses by a health professional either in person or via telemedicine. The 3HP regimen was self administered by the patient. Video observation was conducted via an application named Jabber. Therapy completion was defined as 11 weekly doses of isoniazid and rifapentine taken in a 16 week period, as this is how it was previously defined in the literature.[3,7,8] Demographic and medical history data (age, gender, race/ethnicity, height, weight, BMI, alcohol

use, comorbidities, and medications) were recorded. Adverse events were graded according to guidelines established by the National Cancer Institute's Common Terminology Criteria for Adverse Events.[9] Adverse event rates, drug adherence rates and demographic data were abstracted from the chart review.

The protocol was reviewed by the institutional review board of Cincinnati Children's Hospital Medical Center and determined to be exempt in accordance with applicable regulations and institutional policy. Human experimentation guidelines of the US Department of Health and Human Services and those of Cincinnati Children's Hospital Medical Center were followed in the conduct of this research.

Results

A total of 22 participants who received 3HP therapy between January 2017 and June 2019 were included in this retrospective chart review. Of the 22 participants who received 3HP with DOT, 10 patients (45%) experienced one or more adverse drug reactions (ADR) (Table 1). The race/ethnicity of the patients differed between those who experienced an ADR and those that did not. Asians (n = 2, 20%) and Hispanic/Latinos (n = 1, 10%) experienced an ADR less often than Whites (n = 3, 30%) and African Americans/Blacks (n = 4, 40%). Otherwise, gender, age, and BMI did not differ between the two groups. Two patients required termination of therapy due to intolerable ADRs, and four patients required medical intervention for the ADR. Eight out of ten patients who experienced an ADR experienced it in the first dose of medication. All eight who experienced an ADR in the first week experienced another ADR in subsequent doses. Both patients who terminated therapy had an ADR during the first week. Medical intervention frequently included anti-nausea medication, and in one case included hospitalization for anaphylaxis. Of note, two patients experienced Grade 3 ADRs: anaphylaxis and significant

weight loss. All patients who experienced an ADR experienced at least one gastrointestinal (GI) ADR with nausea being the most common. Six patients experienced nausea, four patients experienced abdominal pain, four patients experienced vomiting, and two patients experienced weight loss. Weight loss was reversed upon cessation of the therapy. Other side effects included diarrhea, headache, anorexia, dermatologic effects, neurotoxicity, fever, and influenza syndrome. Of the patients who experienced an ADR, 80% experienced their first ADR during the first week. On average, the ADR lasted for a duration of 3.4 weeks.

Discussion

In this retrospective chart review, pediatric patients ages 2 to 20 years receiving 3HP with DOT for latent tuberculosis at our institution experienced a higher adverse event rates and more severe adverse events. [3,7,8] The difference in racial distribution among our population compared to other studies is not previously described and warrants further investigation. Specifically, the subjects in the other studies were composed of a relatively greater proportion of Hispanic/Latino participants and a relatively lesser proportion of White and Black/African American participants as compared to the children in our study (Table 1).

One potential explanation of these findings is that this study's cohort and those utilized in previous studies differed in the race/ethnicity of the participants included in the study.[3,7,8] The race/ethnicity differed between those who experienced an ADR and those that did not, as Whites and African Americans/Blacks more often experienced an adverse drug event as compared to Hispanic/Latino and Asian patients. While conclusions are difficult to ascertain from this small cohort, further study is warranted to better understand the association of race/ethnicity with tolerability of the 3HP regimen. Currently, there is lack of literature on the differences in ADRs by race in populations receiving pharmacologic treatment for latent tuberculosis.

To our knowledge, this is the first case series to report a high rate of ADRs and treatment discontinuation in pediatric patients receiving 3HP with DOT for latent tuberculosis. Potential limitations include the small number of cases and the lack of data collected on 9H safety and efficacy at CCHMC. However, the high adverse event rate and treatment discontinuation rate suggest that we should continue to monitor this regimen for its safety and tolerability in some pediatric populations. This information may be useful in guiding clinical practice, as healthcare providers should proceed with caution if patients experience an adverse reaction during the initial dose of therapy and should be monitoring patients for the common side effects reported in this study. In sum, our findings suggest that 3HP with DOT may be tolerated differently in some populations and may warrant continued study.

References

1. Houben RMGJ, Dodd PJ. The Global Burden of Latent Tuberculosis Infection: A Re-estimation Using Mathematical Modelling Metcalfe JZ, editor. PLOS Medicine. 2016;13(10):e1002152. doi:10.1371/journal.pmed.1002152

2. Miramontes R, Hill AN, Yelk Woodruff RS, Lambert LA, Navin TR, Castro KG, LoBue PA. Tuberculosis Infection in the United States: Prevalence Estimates from the National Health and Nutrition Examination Survey, 2011-2012 García-García J-M, editor. PLOS ONE. 2015;10(11):e0140881. doi:10.1371/journal.pone.0140881

3. Villarino ME, Scott NA, Weis SE, Weiner M, Conde MB, Jones B, Nachman S, Oliveira R, Moro RN, Shang N, et al. Treatment for Preventing Tuberculosis in Children and Adolescents. JAMA Pediatrics. 2015;169(3):247. doi:10.1001/jamapediatrics.2014.3158

4. Centers for Disease Control and Prevention. Recommendations for use of an isoniazid-

rifapentine regimen with direct observation to treat latent Mycobacterium tuberculosis infection. MMWR. Morbidity and mortality weekly report. 2011;60(48):1650–3.

5. Sterling TR, Villarino ME, Borisov AS, Shang N, Gordin F, Bliven-Sizemore E, Hackman J, Hamilton CD, Menzies D, Kerrigan A, et al. Three Months of Rifapentine and Isoniazid for Latent Tuberculosis Infection. New England Journal of Medicine. 2011;365(23):2155–2166. http://www.nejm.org/doi/abs/10.1056/NEJMoa1104875. doi:10.1056/NEJMoa1104875

6. Borisov AS, Bamrah Morris S, Njie GJ, Winston CA, Burton D, Goldberg S, Yelk Woodruff R, Allen L, LoBue P, Vernon A. Update of Recommendations for Use of Once-Weekly Isoniazid-Rifapentine Regimen to Treat Latent *Mycobacterium tuberculosis* Infection. MMWR. Morbidity and Mortality Weekly Report. 2018;67(25):723–726. http://www.cdc.gov/mmwr/volumes/67/wr/mm6725a5.htm?s_cid=mm6725a5_w. doi:10.15585/mmwr.mm6725a5

7. Cruz AT, Starke JR. Completion Rate and Safety of Tuberculosis Infection Treatment With Shorter Regimens. Pediatrics. 2018;141(2):e20172838. http://www.ncbi.nlm.nih.gov/pubmed/29363561. doi:10.1542/peds.2017-2838

8. Cruz AT, Starke JR. Safety and Adherence for 12 Weekly Doses of Isoniazid and Rifapentine for Pediatric Tuberculosis Infection. The Pediatric Infectious Disease Journal. 2016;35(7):811–813. http://insights.ovid.com/crossref?an=00006454-201607000-00028. doi:10.1097/INF.0000000000001164

9. Cancer Institute N. Common Terminology Criteria for Adverse Events (CTCAE) Common Terminology Criteria for Adverse Events (CTCAE) v5.0. 2017.

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