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Analysis of severe adverse events reported among patients receiving isoniazid-rifapentine treatment for latent *Mycobacterium tuberculosis* infection — United States, 2012–2016

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Abstract

We analyzed data from 2012–2016 for patients who were hospitalized or who died after ≥1 dose of isoniazid-rifapentine for treatment of latent *Mycobacterium tuberculosis* infection. No patients died; 15 were hospitalized. Nine patients experienced hypotension and 5 had elevated serum aminotransferases, reinforcing the need for vigilant monitoring during treatment.

Keywords

tuberculosis; latent; adverse; isoniazid; rifapentine

Background

Approximately 13 million people in the United States are estimated have latent *Mycobacterium tuberculosis* infection (LTBI) [1]. Without treatment, 5 to 10% of infected

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Potential conflicts of interest

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persons will develop tuberculosis disease [2], and >80% of tuberculosis cases in the United States are attributable to reactivation of LTBI [3]. Therefore, LTBI treatment has been a cornerstone of the U.S. strategy for TB elimination [4, 5]. Unfortunately, medications to treat LTBI are not without potential adverse effects, so monitoring throughout treatment is recommended [5].

Until more recent recommendations for 12 doses of isoniazid-rifapentine [6, 7], 6–9 months of isoniazid had been the mainstay of treatment for LTBI. However, given concerns regarding hepatoxicity and the long duration of treatment, safer, shorter-course regimens had long been desired. In 2000, based on promising results from clinical trials, the American Thoracic Society and Centers for Disease Control and Prevention (CDC) recommended use of the 2-month regimen of rifampin-pyrazinamide [5]. However, shortly thereafter, CDC received reports of severe liver injury and deaths associated with use of rifampin-pyrazinamide, and in response initiated emergency surveillance to monitor adverse events associated with this regimen [8]. These surveillance data and additional study led to revised recommendations so that by 2003, this regimen generally was not offered [9], and isoniazid remained the mainstay of LTBI treatment. In 2004, CDC expanded surveillance to include severe adverse events associated with any LTBI treatment regimen, initiating the National Surveillance for Severe Adverse Events system. Subsequently, CDC received reports of severe liver injury, including death, among patients who received isoniazid [10], and pursuit for an alternative regimen continued.

Finally, based on results from three randomized controlled trials, in 2011, CDC recommended 12 weekly doses of isoniazid-rifapentine administered by directly observed therapy as an equal alternative to 9 months of isoniazid for otherwise healthy persons ≥12 years old [6]. In 2018, CDC updated these recommendations to include self-administration for persons ≥2 years old and certain persons with human immunodeficiency virus (HIV) infection [7]. This report summarizes surveillance data reported to CDC during 2012–2016 for severe adverse events associated with use of isoniazid-rifapentine for LTBI treatment.

Methods

For surveillance purposes, a severe adverse event was defined as hospitalization or death after ≥1 dose of isoniazid-rifapentine for LTBI treatment. Events were typically reported by treating clinicians to health departments, who then notified CDC. After initial recommendations for use of isoniazid-rifapentine, CDC initiated an observational cohort of LTBI patients receiving this regimen through 16 U.S. tuberculosis control programs [11]. In order to facilitate the usual reporting pathway of severe adverse events to CDC, investigators from this postmarketing project notified both CDC's National Surveillance for Severe Adverse Events system and state health departments of patients who died or were hospitalized. Because the quality and quantity of information reported to CDC's surveillance system varied, to better characterize patients and events, CDC sought invitations to conduct on-site investigations that included medical record reviews and interviews with patients or their proxies and clinicians involved in their care. Upon invitation by reporting jurisdictions, a CDC nurse epidemiologist and/or medical officer collected information on-site about

patient demographics, treatment course, clinical symptoms, dates of hospitalization, clinical testing results, and clinical outcome.

Results

CDC received no reports of deaths but received reports of hospitalization for 24 patients; 22 of these patients were initially recognized by the postmarketing project. CDC conducted on-site investigations for 20 patients, all initially recognized by the postmarketing project. Of the 20 severe adverse events for which an investigation was conducted, 5 were deemed by the treating clinical team or the CDC investigators as not being related to the isoniazid-rifapentine regimen. Of the 15 remaining patients, the age distribution was between 20–79 years (Table 1). Eight patients were male. Of 10 patients for whom country of birth was known, 2 were born outside of the United States. Nearly half underwent testing for LTBI for administrative purposes (e.g., employment, long-term care residence), the most common reason for testing. Four patients underwent testing for either a medical risk factor (n=2) or recent tuberculosis exposure (n=2). One patient had HIV infection, 1 had hepatitis C virus infection, and 3 had diabetes mellitus. Seven patients were taking >3 medications to treat other health conditions (median: 3, range: 0–15) at the time of LTBI treatment initiation.

Ten patients received ≤4 doses of isoniazid-rifapentine (median: 3, range 1–7) before hospitalization. Of 12 patients for whom time between last dose and onset of symptoms was known, duration was ≤6 hours for 6 patients and >48 hours for 4 patients. Over half (n=8) experienced an escalation of symptoms with subsequent doses before hospitalization. Subjective fever or nausea, each reported by two-thirds of patients, were the most common presentation features; seven patients who reported subjective fever had temperature measured >38.3 C during hospital evaluation. Nine patients had systolic blood pressure <90 mm Hg upon presentation leading to hospitalization, 5 of whom were noted in medical records to have received intravenous fluid repletion; none required vasopressor support. Of 13 patients with serum aminotransferase and creatinine levels reported, 5 had serum aminotransferases ≥twice the upper limit of normal (ULN), including 2 with levels ≥5 times ULN, and 3 had acute kidney injury (i.e., an increase of ≥0.3 mg/dl in serum creatinine or >50% increase in serum creatinine from baseline). Two of 7 patients with reported values had an International Normalized Ratio (INR)>1.5. Overall, 8 patients were hospitalized for >48 hours. Three patients underwent re-challenge to isoniazid-rifapentine; 1 of these patients tolerated re-challenge and completed treatment and 2 did not tolerate retreatment with this regimen but did tolerate treatment with an alternative regimen for LTBI (1 treated with rifampin and 1 treated with isoniazid). All patients survived to discharge and recovered without sequelae as of the time of investigation.

Discussion

This is the first report from CDC’s surveillance for severe adverse events associated with use of isoniazid-rifapentine for LTBI treatment. In contrast to previous reports of severe liver injury or death associated with isoniazid or rifampin-pyrazinamide [8–10], CDC received no reports of deaths or irreversible organ failure associated with use of isoniazid-rifapentine. Although over half of patients in this series experienced hypotension—a potentially life-

threatening adverse effect—all responded to LTBI treatment discontinuation and supportive therapy without vasopressors and recovered without sequelae. Liver injury, observed in over a third of patients in this series who had transaminase levels recorded, has been reported in association with use of isoniazid-rifapentine. However, no patients in this or other reports have died or required liver transplantation, and rates of liver injury reported in clinical trials have been less than with isoniazid alone [12, 13].

Although surveillance data in combination with research findings have previously led to key changes in recommendations for LTBI treatment [9], surveillance data alone have limitations. First, underreporting is common in passive reporting systems such as this one. Indeed, 92% of events were detected first by the postmarketing surveillance project, which provided active enhancement of an otherwise passive system. Consequently, these surveillance data probably capture a small subset of patients, and their representativeness is not known. Second, the denominator for the total number of patients receiving isoniazid-rifapentine regimen during this time period is not known making it impossible to determine frequency of severe adverse events on this regimen. Third, the small number of cases limits inferences that can be made from findings. Fourth, attribution of a drug reaction in the absence of a confirmatory test is a diagnosis of exclusion, so determining a true association can be difficult, especially in the presence of comorbid conditions or plausible alternative etiologies.

Despite these limitations, these surveillance data provide useful information to characterize severe adverse events associated with isoniazid-rifapentine, and in combination with data from clinical trials and other studies [11–14], provide reassurance about the regimen's overall safety. However, as illustrated by these and other data, potentially life-threatening effects, such as hypotension, can occur with use of this regimen, underscoring extant recommendations for clinical monitoring and patient education. Although most patients had received ≤4 of 12 doses before hospitalization, one had received 7. Further, drug reactions can be idiosyncratic. Therefore, monitoring is needed throughout treatment, not just early on [6, 7]. Even in recognition of maintaining clinical vigilance throughout treatment, these data further illustrate the promise of the 12-dose regimen of isoniazid-rifapentine to facilitate LTBI treatment, a key component of tuberculosis elimination in the United States.

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Table 1.

Demographic and clinical characteristics of patients hospitalized after ≥1 dose of isoniazid-rifapentine for treatment of latent tuberculosis infection (LTBI) thought likely or possibly related to medication use — United States, 2012–2016 (N=15)

Characteristic	Number	(%)
Age at LTBI treatment initiation		
<20 years	0	(0)
20–29 years	3	(20.0)
30–39 years	2	(13.3)
40–49 years	2	(13.3)
50–59 years	3	(20.0)
60–69 years	2	(13.3)
70–79 years	3	(20.0)
>79 years	0	(0)
Sex		
Male	8	(53.3)
Female	7	(46.7)
Country of birth		
U.S.-born	8	(53.3)
Non-U.S.-born	2	(13.3)
Unknown	5	(33.3)
Race/ethnicity		
White, non-Hispanic	8	(53.3)
Black, non-Hispanic	3	(20.0)
Hispanic	1	(6.7)
Asian	1	(6.7)
Other/Unknown	2	(13.3)
Behavioral or social risk factors for tuberculosis		
Homeless within year of LTBI testing	0	(0)
Resident of correctional facility at the time of LTBI testing or treatment	0	(0)
Daily Alcohol use	0	(0)
Reason for LTBI testing		
Administrative requirement	7	(46.7)
Medical risk factor for tuberculosis	2	(13.3)
Contact to a person with tuberculosis	2	(13.3)
Other	4	(10)
Comorbid conditions		
Any medical condition	11	(73.3)
Human immunodeficiency virus infection	1	(6.7)
Hepatitis C virus infection	1	(6.7)
Diabetes	3	(20.0)
Cardiovascular disease	7	(46.7)

Characteristic	Number	(%)
Concomitant hepatotoxic medication use[a]	9	(60.0)
Time between last dose and onset of symptoms leading to hospitalization		
≤6 hours	6	(40)
>6 but ≤12 hours	1	(6.7)
>12 hours but ≤24 hours	0	(0)
>24 hours but ≤36 hours	1	(6.7)
>36 hours but ≤48 hours	0	(0)
>48 hours	4	(26.7)
Unknown	3	(20)
Escalation of symptoms with subsequent doses before hospitalization	8	(53.3)
Features of presentation leading to hospitalization		
Presenting symptoms		
Subjective fever	10	(66.7)
Nausea	10	(66.7)
Headache	7	(46.7)
Subjective rash	2	(13.3)
Dizziness or fainting	6	(40.0)
Presenting signs		
Fever (temperature > 38.3 C)	7	(46.7)
Rash noted on exam	2	(13.3)
Hypotension[b]	9	(60.0)
Laboratory findings		
Liver injury[c]	5	(38.5)[d]
Acute kidney injury[e]	3	(23.1)[f]
Coagulopathy[g]	2	(28.6)[h]
Duration of hospitalization		
≤24 hours	2	(13.3)
25–48 hours	5	(33.3)
>48 hours	8	(53.3)
Re-challenged with isoniazid-rifapentine following hospitalization		
Yes	3	(20.0)
Tolerated	1	
Did not tolerate	2	
No	7	(46.7)
Unknown	5	(33.3)

[a]Concomitant medications with a LiverTox likelihood score of A or B for causing drug-induced liver injury were considered hepatotoxic (https://www.ncbi.nlm.nih.gov/books/NBK547852/)

[b]Systolic blood pressure <90 mm Hg.

[c]Alanine aminotransferase ≥twice upper limit of normal.

[d]Percentage based on 13 patients with serum aminotransferase levels recorded.

[e] Increase of ≥0.3 mg/dl in serum creatinine or >50% increase in serum creatinine from baseline.

[f] Percentage based on 13 patients with serum creatinine levels recorded.

[g] Elevation of the International Normalized Ratio (INR) >1.5.

[h] Percentage based on 7 patients with INR level recorded.