Journal of Microbiology, Immunology and Infection (2018) xx, 1–5

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Brief Communication

Three months of rifapentine and isoniazid for latent tuberculosis infection in hemodialysis patients: High rates of adverse events☆

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Received 1 February 2018; received in revised form 21 April 2018; accepted 7 May 2018
Available online ■ ■ ■

KEYWORDS
Rifapentine;
3HP;
Latent tuberculosis;
LTBI;
Hemodialysis

Abstract The consequences of once-weekly rifapentine plus isoniazid for 3 months (3HP) against latent tuberculosis infections in hemodialysis patients have not been studied before. This is the first study to evaluate the safety and tolerability of 3HP in this population and revealed a completion rate of 65.4%. The therapy was not associated with hepatotoxicity, but with high rates of adverse events (69.2%).

☆ This manuscript has be presented in the part of Paper Poster at 28th ECCMID, 21–24 April 2018; Madrid, Spain.

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https://doi.org/10.1016/j.jmii.2018.05.003

Introduction

Patients with end-stage renal disease (ESRD) requiring hemodialysis (HD) are considered a risk group for tuberculosis (TB) infection.[1] Treatment of latent tuberculosis infection (LTBI) among the people at high risk for progression to active disease is an important strategy for TB control and elimination The WHO has recommended that patients receiving dialysis should be tested for treatment of LTBI.[2]

Once-weekly rifapentine plus isoniazid for 3 months (3HP) is an effective regimen against LTBI.[3,4] Compared with 9 months of daily isoniazid, 3HP is associated with a lower hepatotoxicity rate,[3–5] but more common systemic drug reactions.[4,5] Although previous studies have demonstrated that 3HP can, with adequate safety and tolerability, decrease the risk of active TB in persons with LTBI, ESRD patients on HD have not been studied.[4–6] Therefore, we conducted a study to assess the tolerability and safety of the 3HP regimen in ESRD patients on HD.

Methods

We prospectively assessed ESRD patients receiving HD thrice weekly and who started treatment for LTBI in Kaohsiung medical university hospital and Kaohsiung municipal Ta-Tung hospital between March and November 2017. The study was reviewed and approved by the Institutional Review Board (IRB. No. KMUHIRB-EXEMPT(I)-20170020). Patients with positive interferon-gamma release assays (IGRAs) were evaluated by infectious disease specialists. LTBI diagnosis was defined as a positive the IGRA testing (a QuantiFERON value of at least 0.35 is considered positive), a chest radiograph without typical presentations of active TB, and an absence of history of TB.

Once weekly isoniazid (15 mg/kg/dose; maximum 900 mg) and rifapentine (>50 kg: 900 mg) were given for 12 weeks to patients after hemodialysis with direct observation therapy (DOT).[4] Four TB case managers provided DOT once weekly at outpatient infectious disease clinics. Demographic data, adverse events (AEs), reasons for discontinuation, laboratory results and medication records were collected using a standardized data collection form. Liver function tests and complete blood cell counts were obtained at the baseline and then twice monthly during treatment. The potential drug—drug interactions for each patient were recorded before starting 3HP therapy.[4,7]

All AEs from patients who received ≧1 dose of the 3HP regimen were included for analysis. Severe AEs were defined as those resulting in hospitalization, hypotension or loss of consciousness, anaphylaxis, or grade 4 toxicity.[5] Flu-like symptoms were defined as presenting with fever or chills and weakness, fatigue or muscle pain and aches, syncope, tachycardia, palpitations, flushing, dizziness, conjunctivitis, or sweats.[5] The categorical variables were analyzed using Fisher's exact test, and a p-value <0.05 was considered significant.

Results

The demographic characteristics of ESRD patients receiving HD are shown in Table 1. A total of 26 subjects (mean age, 63.8 ± 12.2 years, 61.5%≧65 years; male, 69%) with long-term dialysis (mean length of HD use, 6.8 ± 6.2 years) were enrolled. The common comorbidities were hypertension and diabetes.

The overall completion rate was 65.4% (17/26). Their blood biochemistry values were examined before 3HP therapy, during treatment and after completing the treatment (Supplementary Table 1). No hepatotoxicity was detected among HD patients. All patients had anemia before initiating 3HP therapy, and the followup data in most of them during treatment were stable.

Eighteen of 26 (69.2%) patients had AEs. The most common AEs were fatigue, fever and vomiting (Fig. 1). The reason for incomplete treatment in these patients ($n = 9$) was intolerance of AEs. There was a higher proportion of vomiting in the incomplete treatment group ($p = 0.034$). However, most AEs were mild, and only two severe AEs were recorded (7.7%) (Supplementary Table 2). Patient No. 22 took 3HP once, followed by slow responsiveness and progressive confusion 3 h later, but totally recovered three days later without neurological sequel. Patient No. 25 had taken nifedipine for hypertension control and suffered from a hypertensive crisis after taking 3HP once. The blood pressure became relatively stable after discontinuing 3HP seven days later. Except for this case, there was no further dosing adjustment reported in patients with hypertension or hyperlipidemia.

Discussion

To our knowledge, this is the first study to evaluate the safety profiles of 3HP on HD patients. The completion rate of 3HP supervision by DOT in a HD population is 65.4%. This HD population included a high proportion of elderly patients (61.5% ≧ 65 years) and comorbidities. A safety profile revealed that most AEs were mild, and the most common AEs were fatigue, fever and vomiting. No hepatotoxicity or death attributable to the study drugs was reported. This regimen has an acceptable safety record in an HD population.

Only 8.2% of AEs were reported in PREVENT TB trials, and 35.7% of AEs were reported in the post-marketing study.[3,4] In a previous study in Taiwan, 43.6% of patients reported AEs with 3HP treatment.[6] Our study revealed 69.2% of HD patients reported AEs during treatment, and the most common AEs were fatigue, fever and vomiting, which were similar to the results of previous studies.[3,6] Four grade 3 or 4 AEs were reported, and three AEs were based on neurological symptoms (Supplementary Table 2). However, no such AEs were recorded in a prospective daily 300 mg isoniazid 1-year prophylaxis trial conducted in an HD population.[8] Because the neurological symptoms were not major AEs in previous 3HP studies,[3–5] this phenomenon needs further study to evaluate whether such neurologic AEs are related to the high dose of isoniazid, especially in a HD population.[9] Hepatotoxicity (50%) was the main

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Table 1 Patients' characteristics and medication reactions after any 3HP dose (n = 26).[a]

Patient no.	Age	Sex	HD duration, yr	Comorbidities	BMI	Main concurrent medication	Dose received	Main events or reason for discontinuation
1	52	m	3	HTN, DM	22.8		12	No AEs
2	49	m	13	HTN, CAD	21.5		12	No AEs
3	77	m	1	HTN, DM	21.2	Repaglinide, saxagliptin	12	Dizziness for one day after each dose
4	69	f	16	Cancer	19.0		12	Fatigue for half day after each dose
5	76	m	14	HTN, DM	21.0		12	Facial palsy developed after 6th dose
6	49	f	1	HTN, HLD, DM	24.2	Atorvastatin, carvedilol	12	Mild HTN developed in first two doses then stabilized in later doses
7	66	m	17	HTN, HLD, DM, CAD	22.2	Atorvastatin, propranolol	12	No AEs
8	54	m	2	HTN, HDL, DM, CAD	31.7	Rosuvastatin, linagliptin	12	GI discomfort after each dose
9	41	m	1	HTN, Cancer	27.7	Clonidine, amlodipine/ valsartan, labetalol,	12	No AEs
10	83	f	5	HTN, DM, CAD, RA	24.0		12	Dizziness, fatigue after each dose
11	65	m	5	HTN, HLD, DM, CAD	21.4	Atorvastatin	12	Flu-like symptoms developed after 3rd dose; the symptoms improved after 5th dose
12	47	m	3	HTN	29.8		12	Flushing developed after 3rd and 4th doses
13	76	m	14	HTN, DM	27.5	Saxagliptin	12	No AEs
14	80	f	2	DM, HCV	23.9		12	No AEs
15	76	m	12	HTN, DM	24.1		12	No AEs
16	38	f	1	HTN	34.9	Bisoprolol, valsartan	12	Fever and skin rash developed after 3rd and 4th dose
17	76	m	4	HCV	25.8		12	No AEs
18	63	m	19	HTN	20.9		1	Severe dizziness after one dose
19	65	m	10	HTN	21.5		6	Flu-like symptoms developed after 3rd dose; discontinuing treatment due to severe vomiting
20	66	m	17	HTN, HLD, DM	24.5	Repaglinide, bisoprolol, fenofibrate	8	Flu-like symptoms developed after taking 3HP since 3rd dose
21	70	m	1	HTN, HLD, DM, CAD, CVA	24.9	Amlodipine, atorvastatin, repaglinide	5	Flu-like symptoms developed after 4th dose
22	69	f	3	HTN, DM	26.7		1	Progressive confusion after one 3HP dose
23	58	m	1	HTN, CAD	26.4		8	GI discomfort after each 3HP dose; discontinuing 3HP due to severe vomiting finally
24	63	f	2	HTN, HCC, LC, HCV	22.9		4	Pancytopenia was noted before 3HP therapy. Progressive pancytopenia, but the hemogram was not recovered after discontinuing 3HP
25	65	f	5	Cancer, HTN	16.8	Nifedipine	1	Hypertension crisis after one dose
26	67	m	5	HTN, DM, CVA	26.0	Carvedilol, saxagliptin, amlodipine	1	Appetite loss and fatigue after one dose

[a] Patients could report ≧1 reaction after taking ≧1 dose. Abbreviations: AE, adverse event; BMI, body mass index; CAD, coronary artery disease; CVA, cerebrovascular accident; DM, diabetes mellitus; f, female; GI, gastrointestinal; HCV, hepatitis C virus infection; HLD, hyperlipidemia; HTN, hypertension; LC, liver cirrhosis; m, male; RA, rheumatoid arthritis; 3HP, Three months of rifapentine and isoniazid.

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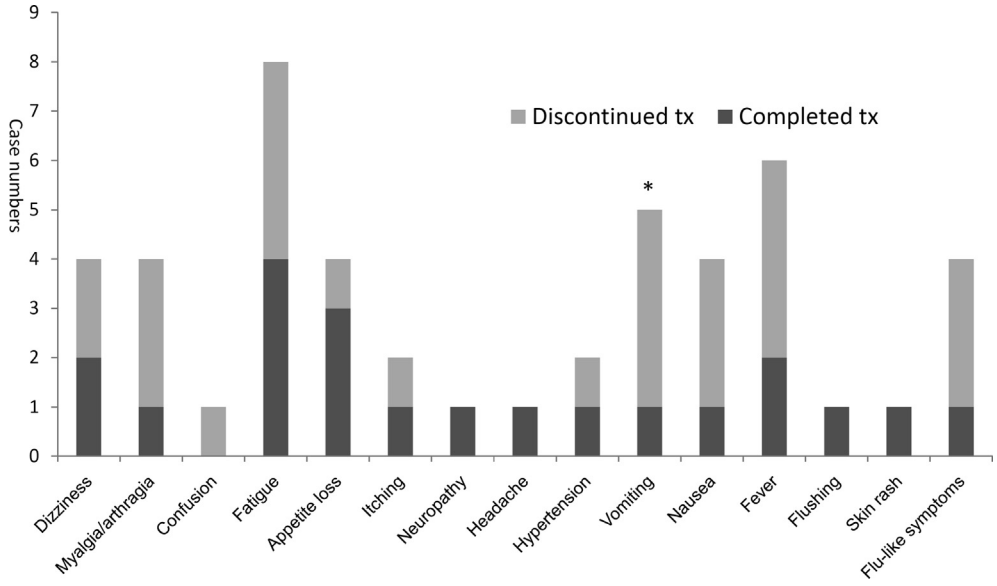

Figure 1. Numbers of patients with adverse events after taking 3HP dose. Patients could report ≧1 reaction after taking ≧1 dose. *$p = 0.034$. Abbreviations: Tx, treatment; 3HP, Three months of rifapentine and isoniazid.

concern in a previous isoniazid prophylaxis trial in a HD population,[8] and this AE was significantly lower during a 3HP regimen.[4,6] In contrast, no hepatotoxicity was detected in our study.

Rifapentine may increase the metabolism and decrease the serum concentration of calcium channel blockers (CCB) and HMG-CoA reductase inhibitors.[4,7] Simkin J et al. reported that 22% of renal transplant candidates taking antihypertension drugs developed severe hypertension after 3HP therapy.[10] However, our study revealed that only one case (3.8%) suffered from uncontrolled blood pressure after one administration of 3HP, which may be potentially related to a drug—drug interaction between rifapentine and the CCB.

3HP supervision by DOT improves compliance in the treatment of LTBI.[3,4,6] Both DOT and a shorter duration of treatment probably explain the high treatment completion rate. The completion rate in this HD population was lower than in previous studies.[3,4,6] Among the patients who did not complete treatment (n = 9), only two (22.2%) were due to severe AEs, and the higher proportion reported vomiting as the reason for discontinuing treatment ($p = 0.034$). Aside from drug-related AEs, the possible reason for a high discontinuation rate is that HD patients have high rates of comorbidities and tend to be older in our study. Therefore, enhancing adherence and increasing completion rates in HD patients would require not only the management of AEs but also the integration of other strategies, such as intensive case management, psychosocial supports, and provision of incentives.

In conclusion, the completion rate of 3HP therapy was 65.4% in HD patients in our study. A safety profile revealed that most AEs were mild, and the most common AEs were fatigue, fever and vomiting. This regimen has an acceptable safety record in an HD population but there is a lack of sufficient data on the efficacy for this group, and more substantial evidence is needed.

Conflict of interest statement

The authors declare that they have no conflict of interest.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.jmii.2018.05.003.

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