Established in 1871
Swiss Medical Weekly
Formerly: Schweizerische Medizinische Wochenschrift
The European Journal of Medical Sciences

Original article | Published 15 August 2011, doi:10.4414/smw.2011.13240
Cite this as: Swiss Med Wkly. 2011;141:w13240

Adverse effects and adherence to treatment of rifampicin 4 months vs isoniazid 6 months for latent tuberculosis

A retrospective analysis

Isabelle Fresard, Pierre-Olivier Bridevaux, Thierry Rochat, Jean-Paul Janssens

Division of Pneumology, Geneva University Hospitals, Switzerland

Summary

AIM OF STUDY: To compare rates of treatment interruption because of side effects and completion rates between subjects treated for latent tuberculosis infection (LTBI) by isoniazid (INH) for 6 months and subjects treated with rifampicin (RIF) for 4 months.

METHODS: Retrospective analysis of all patients treated for LTBI by INH (1993–2002) or RIF (2004–2007) based on a database including age, gender, prior liver diseases, alcohol consumption, completion rates, time and cause of interruption and monthly analysis of ASAT and ALAT.

RESULTS: 624 subjects were included, 426 treated by INH and 198 by RIF. Gender, origin, history of prior hepatic disease and alcohol excess did not differ between groups. Treatment interruption because of hepatotoxicity was significantly higher in the INH group than in the RIF group (6.1% vs 2.0%; p = 0.03). Completion of treatment was significantly higher in the RIF group compared to the INH group (83% vs 74%; p = 0.02).

CONCLUSION: A 4-month RIF treatment was associated with significantly less interruption of treatment because of hepatotoxicity and higher completion rates compared to a 6-month INH regimen. These results support the RIF regimen as an alternative to the presently recommended 9 months of INH in clinical practice.

Key words: *tuberculosis; latent tuberculosis infection; treatment; rifampicine; isoniazid*

Introduction

The treatment of latent tuberculosis infection (LTBI) is an essential part of tuberculosis control, especially in countries with a low incidence of tuberculosis where most cases of active tuberculosis are reactivations of LTBI [1].

After an initial recommendation of a 12-month isoniazid (INH) regimen for treatment of LTBI, a 6-month regimen was recommended as of 1965 because of lower completion rates with longer treatments. A later revision of original data led to a recommendation of a prolonged (9 months) treatment of INH [1, 2].

The potential disadvantages of this treatment were hepatotoxicity and adherence. Potentially fatal hepatitis associated with INH was first recognised in the 1970's [3, 4], leading to the recommendation of implementing clinical and laboratory monitoring for patients with possible liver disorders or older than 35 years. Adherence is also an important problem with the 9 months INH regimen: published data suggest that only 59–76% of patients complete this regimen [5–8], albeit for one study on a pharmacist-managed clinic for treating LTBI in health care workers reporting a 93% completion rate [9].

One alternative regimen is rifampicin (RIF) for 4 months: it has been shown to be less hepatotoxic and associated with a better adherence than INH in recent non-randomised studies [10, 11]. In a double-blind placebo-controlled trial published in 1992 [12], RIF-induced hepatotoxicity was not higher than that of a placebo. A recent randomised open-label study [7], described less serious adverse effects and better adherence with a RIF regimen compared to INH. However, this randomised trial included highly motivated patients, thus limiting conclusions applicable for everyday practice.

When international and national (Swiss) guidelines recommended extending the duration of treatment for LTBI with INH from 6 to 9 months, the TB-clinic of Geneva University Hospitals opted for a 4-month treatment with RIF as default treatment for LTBI, mainly because we anticipated a drop in compliance with the 9-month regimen. Because all patients followed at our TB-clinic were included in a computerised database, we thus had the possibility of comparing – in the same clinical environment – 2 successive periods in terms of side effects and adherence to treatment: a "6-month of INH" [13] followed by a "4-month of RIF" period.

Our hypothesis was that a) RIF would be less hepatotoxic than INH and better tolerated, and b) adherence to RIF would be better than adherence to INH, even taken for 6 months.

Methods

Study design and setting

All patients treated for LTBI in the outpatient clinic of the Division of Pneumology, Geneva University Hospitals during the study period were included in a computerised database which collected items such as: gender, age, country of birth, self-reported alcohol consumption (alcohol excess defined as ≥2 drinks/day), tolerance (results of monthly ASAT: Aspartate amino-transferase; and ALAT: Alanine amino-transferase, reported adverse effects), history of prior hepatic disorders (hepatitis, cirrhosis, jaundice or other known liver disorders) and adherence (assessed by attendance to visits and monthly urinary tests for INH).

This retrospective cohort included all patients treated with INH from January 1993 to December 2002 and those treated with RIF from January 2005 to December 2007. The 6-month INH treatment was prescribed according to prevailing international guidelines from January 1993 to December 2002 [14]. When the recommended duration of INH treatment was extended from 6 to 9 months [1], the alternative regimen of 4 months of RIF was progressively implemented as first line therapy at Geneva University Hospitals. Rifampicin was not prescribed to patients with HIV co-infection treated with HAART because of the potential pharmacological interactions.

The study protocol was accepted by the Ethics Committee of Geneva University Hospitals in June 2008 (N° 08-083R).

Follow-up

Patients were seen on a monthly basis by a physician from the TB-clinic for the whole duration of the treatment. We assumed that patients who attended every month to have their blood tested and their urine analysis (when taking INH), up to the end of their treatment, had a reasonable chance of being adherent to treatment. Prescriptions were renewed every month for one month. No incentives or enablers were used in either study period.

It was the practice of our TB clinic to perform monthly monitoring of ASAT and ALAT in all patients taking either INH or RIF regardless of identified risk factors for liver disorders, age or co-medication. Treatment was discontinued in case of ASAT or ALAT elevation ≥5 times upper limit of normal (ULN) or ≥3 times ULN with symptoms [2].

Outcomes

Outcomes were 1) rate of ASAT or ALAT elevation ≥ than 3 or 5 times above ULN or clinical hepatitis with either regimen; 2) rate of treatment discontinuation because of adverse effects and completion rates and 3) rates of minor adverse reactions with both regimens.

Statistical analysis

Hepatotoxicity was defined as ASAT or ALAT elevation ≥5 times upper limit of normal (ULN) or ≥3 times ULN with symptoms, or as clinical hepatitis [2].

We assessed differences between groups INH and RIF by using parametric, non-parametric and Fischer's exact test for continuous and categorical variables. The relationship between adherence or hepatotoxicity and LTBI therapy was explored with multivariate analysis reporting odds ratio with 95% CI. Models were parsimoniously adjusted for age, sex, nationality, alcohol abuse, history of prior liver disease. These variables were chosen based on their clinical relevance.

Results

Between January 1993 and December 2007, 426 patients were put on 6 months of INH and 198 on 4 months of RIF. Among the 426 patients who started INH, 15 (3.5%) were switched to RIF because of intolerance.

Demographic characteristics of these patients are shown in table 1. Gender, origin, self-reported liver disorders and alcohol excess (>2 drinks/ day) did not differ significantly between groups. Age was slightly higher in the INH group (median age 33 vs. 30 years, p = 0.03), but there was no significant difference between groups as regards the proportion of patients aged ≥35 years.

Drug induced hepatopathy

ASAT/ALAT elevation ≥3 ULN with symptoms occurred in 7 (3.5%) patients taking INH vs. none of the patients taking RIF. Increase of transaminases ≥5 ULN occurred in 19 patients taking INH (4.5%) among whom 6 (1.4%) developed clinical hepatitis. In the RIF group, ASAT/ALAT ≥5 ULN occurred in 4 (2%) patients and there was no clinical hepatitis. Overall, treatment was more often interrupted in the INH group (n = 26; 6.1%) than in the RIF group (n = 4; 2.0%) p = 0.03, because of hepatoxicity (table 2).

ASAT/ALAT elevation (≥3 times ULN) was found in 4.6% (n = 18) of patients aged <35 years and 11.3% (n = 26) of those aged ≥35. In multivariate analysis controlling for age, gender, chronic alcohol use and liver disorders, patients on RIF were twice less likely to experience AST/ALT elevation (≥ 3 times ULN) (OR 0.44 [95% CI 0.20-0.99]) compared to those on INH. Patients aged ≥35 had a two-fold increase in hepatitis (OR 2.47 [95%CI 1.31-4.64]). Alcohol excess (OR 3.30 [95%CI 0.82-13.19]) also tended to be associated with hepatitis.

A multivariate analysis for transaminases elevation ≥5 times ULN was not performed because there were too few patients on RIF with ASAT/ALAT ≥5 times ULN.

Other adverse events

Other adverse events associated with both drugs were cutaneous reactions, gastro-intestinal symptoms other than clinical hepatitis, headache or dizziness, and asthenia. In the INH group, 33 (7.7%) patients developed gastro-intestinal symptoms, 22 (5.2%) asthenia, 5 (1.2%) cutaneous reactions and 8 (2.1%) neurological symptoms. Among the patients taking RIF, 45 (22.7%) had gastrointestinal symptoms, 34 (17.2%) asthenia, 10 (5.1%) cutaneous reactions and 19 (9.6%) neurological symptoms, most often headaches. Thus, there were significantly more minor side effects associated with RIF than with INH but rate of treatment interruption due to these adverse reactions was the same with both drugs (table 2).

Treatment interruption

Adverse reactions led to treatment interruption in 43 (10.1%) patients taking INH: 26 (6.1%) subjects stopped their treatment because of hepatotoxicity and 17 (4%) because of other adverse reactions, with a median time of treatment of 65 days. For patients taking RIF, 15 (7.6%) interrupted their treatment, hepatotoxicity accounted for treatment interruption in 4 cases (2%) and other side effects in 11 cases (5.6%), with a median time of treatment of 26 days. There was a higher rate of interruption of treatment due to hepatotoxicity in the INH group (table 2).

Completion of treatment

Rate of treatment completion (defined as patients who completed 6 months of INH or 4 months of RIF) was significantly higher in the RIF group (n = 164/198; 83%) compared to the INH group (n = 316/426; 74%) (p = 0.03). After controlling for age, gender, alcohol abuse and history of hepatic disorder, patients on RIF were almost twice as likely to complete their treatment compared to those on INH (OR 1.74, CI 95% 1.11–2.72, p = 0.016) (table 3).

Discussion

In this retrospective cohort of patients treated for LTBI, we compared adherence rates and occurrence of adverse effects in patients treated by either 6 months of INH or 4 months of RIF. We found a higher treatment completion rate and a lower occurrence of hepatotoxicity in patients treated with RIF, although minor adverse effects occurred at a similar rate in both groups.

There are 8 published clinical trials documenting the hepatotoxicity of the RIF regimen, with an incidence ranging between 0–1.95% according to the 2006 ATS statement [7, 10–12, 15–18].

Five of these trials compared the rate of hepatotoxicity between the INH and RIF regimens [7, 10–12, 16]. The lower rate of hepatotoxicity induced by RIF in our series is consistent with these previous studies. The transaminases

Table 1: Demographic characteristics of patients with LTBI included at baseline.

	Isoniazid n = 426	**Rifampicin n = 198**	**p-value**
Age, mean (SD)	32 (13)	30 (15)	0.03
Age ≥35 y, n (%)	151 (35.4)	61 (30.8)	0.25
Gender			
Male, n (%)	216 (50.7)	105 (53.0)	0.59
Female, n (%)	210 (49.3)	93 (47.0)	
Origin			
Swiss born, n, (%)	96 (22.5)	48 (24.1)	0.64
Risk factors for liver disorders			
History of prior hepatic disease*, n (%)	7 (1.6)	5 (2.5)	0.46
Alcohol excess, n, (%)	7 (1.6)	4 (2.0)	0.75
* any type of hepatopathy			

Table 2: Adverse events and outcome in patients with LTBI treated with INH or RIF.

	Isoniazid n = 426	**Rifampicin n = 198**	**p-value***
Interruption of therapy due to side effects			
Total, n (%)	43 (10.1)	15 (7.6)	0.35
Treatment changed †	15 (3.5)	0 (0)	0.04
Hepatotoxicity			
Subtotal:	26 (6.1)	4 (2.0)	0.03
ASAT/ALAT ≥3 x <5x ULN	7 (3.5)	0 (0)	0.10
ASAT/ALAT ≥5 x ULN	19 (4.5)	4 (2.0)	0.17
Clinical hepatitis	6 (1.4)	0 (0)	0.18
Others			
Subtotal:	17 (4.0)	11 (5.6)	0.41
Cutaneous reactions	3 (0.7)	4 (2.0)	0.22
Gastro-intestinal symptoms	5 (1.2)	3 (1.5)	0.73
Neurological symptoms	6 (1.4)	4 (2.0)	0.18
Asthenia	3 (0.7)	0	0.55
Interruption of therapy due to non adherence			
Total, n (%)	69 (16.2)	19 (9.6)	0.03
Completion of treatment	316 (74%)	164 (83%)	0.02
† INH switched to RIF in all patients for whom therapy was changed; * Fischer exact test			

Table 3: Odds ratio of treatment completion in patients with LTBI.

	Adjusted* Odds ratio (95% CI)
RIF vs INH	1.74 (1.11–2.72), p = 0.016
Female vs male	1.39 (0.95–2.04), p = 0.09
Alcohol excess vs no alcohol excess	0.39 (0.14–1.10), p = 0.08
History of liver disorder vs no liver disorder	0.40 (0.12–1.34), p = 0.29
*adjusted for age, gender, alcohol excess and history of hepatic disorder	

were routinely monitored in only 4 studies [7, 12, 17, 18] with an incidence of significant transaminase elevation for the RIF group of 1.95% in 1 study [18], and 0–0.7% in the 3 other studies [7, 12, 17]. Moreover, in the study by Menzies et al., transaminases were routinely monitored only at baseline and after 1 and 2 months of treatment. Hepatotoxicity was defined as clinical hepatotoxicity in 4 studies [10, 11, 15, 16] ranging for the RIF treatment between 0 [10] and 0.4% [15]. This could have underestimated the real incidence of significant (according to ATS criteria) transaminase elevation.

Incidence of INH-associated hepatotoxicity was 0.1–0.56% in large retrospective trials [19–21] and 1-4% in smaller trials [7, 22, 23].

Three studies compared the rate of hepatotoxicity between INH and RIF regimens [7, 11, 14], two of these being recent reports. The first one is a large randomised open-label trial by Menzies et al. who found serious hepatoxicity grade 3 (ALAT or ASAT 3–10 times ULN plus symptoms, or ALAT or ASAT 5–10 ULN and no symptoms) and 4 (ALAT or ASAT >10 times ULN) leading to interruption of treatment in 3.8% of patients taking INH and in 0.7% of patients taking RIF [7]. The second one, a large retrospective study, reported that 1.8% of patients in the 9-INH group vs. 0.08% of patients in the 4-RIF group developed hepatotoxicity [11].

Our study shows a higher rate of treatment induced ASAT/ALAT increase for both INH and RIF compared to other authors. This is most probably an artefact which results from the systematic monthly monitoring of ASAT/ALAT, independently from the presence of risk factors for hepatic disease or the occurrence of gastro-intestinal symptoms: we thus detected asymptomatic elevations of ASAT/ALAT which were not reported in other studies. Indeed the higher rate of hepatotoxicity found in our study cannot be explained by age or risk factors for hepatotoxicity when compared to previous publications [7].

Other adverse reactions (gastro-intestinal symptoms, asthenia, transient cutaneous reaction, neurological symptoms) were significantly more frequent among patients taking RIF, but did not lead to interruption of treatment. This is not described in other recent trials [7, 11] and is probably due to the fact that they were transient minor adverse reactions most often not spontaneously reported by the patients. This difference does not seem related to study structure since modalities of clinical follow-up, and length of consultations were similar during both study periods.

Adherence to treatment was significantly better with RIF than INH (OR 1.7, CI 95% 1.11–2.72, p = 0.016). Completion rates for 4-month RIF were 83% vs. 74% with the 6-month INH regimen. For the RIF regimen, completion rates between 72–81% are reported in 3 recent studies [7, 10, 11], which is quite similar to our results. The slightly better adherence in the INH group in our study compared to 53–60% found in the 3 studies described above may result from the shorter duration of therapy (6 months compared to 9) and perhaps also by the monthly clinical and biological follow-up. The completion rate is of major clinical importance since we don't know the efficacy of INH treatment for LTBI if its duration is reduced [1].

There are several limitations to our study. First, it is a retrospective study with two distinct periods of time. However, patient inclusion and clinical management were identical throughout both periods and there were no significant differences in patient characteristics. Also, there was no selection bias because all patients who initiated treatment for LTBI were recorded in our database and included. Secondly, patients were not randomised to the treatment groups, and our comparison is thus a case-control observation without any significant difference between groups for baseline characteristics. Thirdly, INH was given for 6 months instead of the presently recommended 9 month treatment: this was in agreement with guidelines during the study period, and would tend to favour the INH regimen: in spite of this, the RIF regimen was associated with a significantly higher compliance. Finally, baseline data for ASAT/ALAT were not available for all patients (61% had initial ASAT/ALAT baseline values) and are thus not supplied. Also, evaluation of HIV infection and hepatic disorders relies on medical history, since routine testing for prior hepatitis was not recommended in this setting.

In conclusion, in this retrospective study of subjects treated for LTBI, a 4-month RIF treatment was associated with significantly less ASAT/ALAT elevation, less interruption of treatment because of hepatotoxicity and higher completion rates compared to a 6-month INH regimen. Although we still need solid prospective studies to confirm definitively the efficacy of the 4-month RIF for treating LTBI, these results support the RIF regimen as an alternative regimen to the presently recommended 9 months of INH in everyday clinical practice. Furthermore, the absence of RIF-induced hepatotoxicity leading to interruption of treatment suggests that monthly ASAT/ALAT is not necessary in younger subjects (<35) without pre-existing liver disorders.

Funding / potential competing interests: No financial support and no other potential conflict of interest relevant to this article was reported.

Correspondence: *Isabelle Fresard, MD, Division of Pneumology, Geneva University Hospitals, 4, rue Gabrielle-Perret-Gentil, CH-1211 Geneva 14, Switzerland, isabelle.fresard@hcuge.ch*

References

1 Targeted tuberculin testing and treatment of latent tuberculosis infection. This official statement of the American Thoracic Society was adopted by the ATS Board of Directors, July 1999. This is a Joint Statement of the American Thoracic Society (ATS) and the Centers for Disease Control and Prevention (CDC). This statement was endorsed by the Council of the Infectious Diseases Society of America. (IDSA), September 1999, and the sections of this statement. Am J Respir Crit Care Med. 2000;161(4 Pt 2):S221–47.

2 Saukkonen JJ, Cohn DL, Jasmer RM, Schenker S, Jereb JA, Nolan CM, et al. An official ATS statement: hepatotoxicity of antituberculosis therapy. Am J Respir Crit Care Med. 2006;174:935–52.

3 Garibaldi RA, Drusin RE, Ferebee SH, Gregg MB. Isoniazid-associated hepatitis. Report of an outbreak. Am Rev Respir Dis. 1972;106:357–65.

4 Kopanoff DE, Snider DE, Jr., Caras GJ. Isoniazid-related hepatitis: a U.S. Public Health Service cooperative surveillance study. Am Rev Respir Dis. 1978;117:991–1001.

5 Aspler A, Long R, Trajman A, Dion MJ, Khan K, Schwartzman K, et al. Impact of treatment completion, intolerance and adverse events on health system costs in a randomised trial of 4 months rifampin or 9 months isoniazid for latent TB. Thorax. 2010;65:582–7.

6 Menzies D, Dion MJ, Rabinovitch B, Mannix S, Brassard P, Schwartzman K. Treatment completion and costs of a randomized trial of rifampin for 4 months versus isoniazid for 9 months. Am J Respir Crit Care Med. 2004;170:445–9.

7 Menzies D, Long R, Trajman A, Dion MJ, Yang J, Al Jahdali H, et al. Adverse events with 4 months of rifampin therapy or 9 months of isoniazid therapy for latent tuberculosis infection: a randomized trial. Ann Intern Med. 2008;149:689–97.

8 Hess K, Goad J, Wu J, Johnson K. Isoniazid completion rates for latent tuberculosis infection among college students managed by a community pharmacist. J Am Coll Health. 2009;57:553–5.

9 Tavitian S, Spalek V, Bailey R. A pharmacist-managed clinic for treatment of latent tuberculosis infection in health care workers. American Journal of Health-System Pharmacy. 2003;60:1865–61.

10 Lardizabal A, Passannante M, Kojakali F, Hayden C, Reichman LB. Enhancement of treatment completion for latent tuberculosis infection with 4 months of rifampin. Chest. 2006;130:1712–7.

11 Page KR, Sifakis F, Montes de Oca R, Cronin WA, Doherty MC, Federline L, et al. Improved adherence and less toxicity with rifampin vs isoniazid for treatment of latent tuberculosis: a retrospective study. Arch Intern Med. 2006;166:1863–70.

12 A double-blind placebo-controlled clinical trial of three antituberculosis chemoprophylaxis regimens in patients with silicosis in Hong Kong. Hong Kong Chest Service/Tuberculosis Research Centre, Madras/British Medical Research Council. Am Rev Respir Dis. 1992;145:36–41.

13 Langenskiold E, Herrmann FR, Luong BL, Rochat T, Janssens JP. Contact tracing for tuberculosis and treatment for latent infection in a low incidence country. Swiss Med Wkly. 2008;138:78–84.

14 Treatment of tuberculosis and other mycobacterial diseases. Am Rev Respir Dis. 1983;127:790–6.

15 Haley CA, Stephan S, Vossel LF, Sherfy EA, Laserson KF, Kainer MA. Successful use of rifampicin for Hispanic foreign-born patients with latent tuberculosis infection. Int J Tuberc Lung Dis. 2008;12:160–7.

16 Polesky A, Farber HW, Gottlieb DJ, Park H, Levinson S, O'Connell JJ, et al. Rifampin preventive therapy for tuberculosis in Boston's homeless. Am J Respir Crit Care Med. 1996;154:1473–7.

17 Villarino ME, Ridzon R, Weismuller PC, Elcock M, Maxwell RM, Meador J, et al. Rifampin preventive therapy for tuberculosis infection: experience with 157 adolescents. Am J Respir Crit Care Med. 1997;155:1735–8.

18 Fountain FF, Tolley EA, Jacobs AR, Self TH. Rifampin hepatotoxicity associated with treatment of latent tuberculosis infection. Am J Med Sci. 2009;337:317–20.

19 Fountain FF, Tolley E, Chrisman CR, Self TH. Isoniazid hepatotoxicity associated with treatment of latent tuberculosis infection: a 7-year evaluation from a public health tuberculosis clinic. Chest. 2005;128:116–23.

20 LoBue PA, Moser KS. Use of isoniazid for latent tuberculosis infection in a public health clinic. Am J Respir Crit Care Med. 2003;168:443–7.

21 Nolan CM, Goldberg SV, Buskin SE. Hepatotoxicity associated with isoniazid preventive therapy: a 7-year survey from a public health tuberculosis clinic. JAMA. 1999;281:1014–8.

22 McNeill L, Allen M, Estrada C, Cook P. Pyrazinamide and rifampin vs isoniazid for the treatment of latent tuberculosis: improved completion rates but more hepatotoxicity. Chest. 2003;123:102–6.

23 Millard PS, Wilcosky TC, Reade-Christopher SJ, Weber DJ. Isoniazid-related fatal hepatitis. West J Med. 1996;164:486–91.