Low risk of hepatotoxicity from rifampicin when used for cholestatic pruritus: a cross-disease cohort study
Webb, G. J.; Rahman, S. R.; Levy, C.; Hirschfield, G. M.

DOI: 10.1111/apt.14579
License: Creative Commons: Attribution (CC BY)

Document Version
Publisher's PDF, also known as Version of record

Citation for published version (Harvard):
Webb, GJ, Rahman, SR, Levy, C & Hirschfield, GM 2018, 'Low risk of hepatotoxicity from rifampicin when used for cholestatic pruritus: a cross-disease cohort study', Alimentary Pharmacology & Therapeutics, vol. 47, no. 8, pp. 1213-1219. https://doi.org/10.1111/apt.14579

General rights
Unless a licence is specified above, all rights (including copyright and moral rights) in this document are retained by the authors and/or the copyright holders. The express permission of the copyright holder must be obtained for any use of this material other than for purposes permitted by law.

• Users may freely distribute the URL that is used to identify this publication.
• Users may download and/or print one copy of the publication from the University of Birmingham research portal for the purpose of private study or non-commercial research.
• Users may use extracts from the document in line with the concept of ‘fair dealing’ under the Copyright, Designs and Patents Act 1988 (?)
• Users may not further distribute the material nor use it for the purposes of commercial gain.

Where a licence is displayed above, please note the terms and conditions of the licence govern your use of this document.

When citing, please reference the published version.

Take down policy
While the University of Birmingham exercises care and attention in making items available there are rare occasions when an item has been uploaded in error or has been deemed to be commercially or otherwise sensitive.

If you believe that this is the case for this document, please contact UBIRA@lists.bham.ac.uk providing details and we will remove access to the work immediately and investigate.
Low risk of hepatotoxicity from rifampicin when used for cholestatic pruritus: a cross-disease cohort study

G. J. Webb1 | S. R. Rahman1 | C. Levy2 | G. M. Hirschfield1,3

1Birmingham Biomedical Research Centre (BRC), National Institute for Health Research (NIHR), University of Birmingham, Birmingham, UK
2University of Miami, Miami, FL, USA
3Institute of Translational Medicine, Birmingham Health Partners, University Hospitals Birmingham NHS Trust, Birmingham, UK

Correspondence
Dr. GJ Webb, Birmingham Biomedical Research Centre (BRC), National Institute for Health Research (NIHR), University of Birmingham, Birmingham, UK.
Email: gwilym.webb@gmail.com

Funding Information
This report presents independent research funded by the National Institute for Health Research (NIHR). The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health.

Summary

Background: The use of rifampicin for cholestatic pruritus is accompanied by concerns over safety, but the availability of real-world prescribing data is relatively limited.

Aim: We sought to describe the rate and characteristics of rifampicin-induced hepatitis in a mixed aetiology cohort of patients with established liver disease and cholestatic pruritus.

Methods: Retrospective review of records for out-patients commenced on rifampicin for pruritus 2012-2016 inclusive. Rifampicin-induced hepatitis was recorded where alanine aminotransferase activity (ALT) increased to both ≥5 × baseline and ≥5 × upper limit of normal (ULN), or to both ≥3 × baseline and ≥3 × ULN with concurrent elevation in serum bilirubin to ≥2 × baseline and ≥2 × ULN, in addition to a Roussel-Uclaf Causality Assessment Method score of “probable” or “highly probable” for rifampicin causality.

Results: After exclusions, we reviewed 105 patients who took rifampicin for a median of 131 days. Most had primary biliary cholangitis or primary sclerosing cholangitis; 40 (38.1%) were men and median age was 44 years (IQR: 32-57). 44 (41.9%) patients had baseline serum bilirubin ≥2 × ULN and 28 (26.7%) ALT ≥3 × ULN. 5 (4.8%) developed rifampicin-induced hepatitis at a median of 70 (range 27-130) days after drug initiation. No individual or laboratory baseline characteristics were significantly associated with subsequent development of hepatitis. All cases of hepatitis recovered after drug cessation, although one patient was hospitalised and received corticosteroids.

Conclusions: Given the efficacy of rifampicin for an important sub-group of those with cholestatic pruritus, adult patients, including those with jaundice, can be counselled that 95% of prescriptions are safe, and where hepatitis occurs, including at long latency, drug cessation appears effective.
1 | INTRODUCTION

Pruritus is a frequent and distressing complication of liver disease, especially cholestatic liver disease. The antimicrobial drug rifampicin (USAN: rifampin) is recognised as a therapeutic agent for pruritus having shown efficacy in the majority of controlled trials, and is currently recommended by major international guidelines in the therapy of pruritus in cholestatic liver disease.

Rifampicin has been reported to be associated with hepatitis in a minority of patients receiving the drug as therapy for mycobacterial infections. This is especially the case where there is combination therapy with other potentially hepatotoxic agents and is associated with a variety of risk factors. To date meta-analyses of previous controlled studies of rifampicin for pruritus have concluded that the treatment is safe, with the largest study of 61 patients recording no clinically significant episodes of hepatitis. However, despite these meta-analyses, individual reports of rifampicin-induced hepatitis during therapy for pruritus do exist including with occurrence after the short-term follow-up typically used in trials. It remains uncertain as to how best to counsel patients being prescribed rifampicin off-label for therapy of cholestatic pruritus given a lack of estimates regarding its potential to cause liver injury. This is especially the case in those with pre-existing jaundice.

Given the immediate utility to prescribers, we have evaluated the occurrence of hepatitis in a cohort of 105 patients with established liver disease of mixed aetiology in whom rifampicin was prescribed for pruritus. In so doing, we provide real-world data of use to all prescribers when counselling patients.

2 | METHODS

With the permission of University Hospitals Birmingham, a retrospective review of cases notes of all patients attending University Hospitals Birmingham on an out-patient basis from 2012 to 2016 inclusive and who received new prescriptions for rifampicin without concurrent isoniazid was conducted. Details of demographics, laboratory variables and clinical course were reviewed.

Cases were considered to represent rifampicin-induced hepatitis if laboratory values met the criteria of the DILI Expert Working Group:

1. either, a rise in serum aspartate aminotransferase (AST) or alanine aminotransferase (ALT) activity to both $\geq 5 \times$ pre-rifampicin baseline and $\geq 5 \times$ upper limit of normal (ULN);
2. or, a rise in ALT or AST to both $\geq 3 \times$ pre-rifampicin baseline and $\geq 3 \times$ ULN with a concurrent rise in serum bilirubin to both $\geq 2 \times$ pre-rifampicin baseline and $\geq 2 \times$ ULN;
3. and, a Roussel-Uclaf Causality Assessment Method (RUCAM) score of $\geq 6$ (“Probable” or “Highly probable”) for rifampicin hepatitis.

Comparative statistics were used to compare groups that did, and that did not, develop hepatitis whilst taking rifampicin: the chi-squared test was used to compare categorical variables whilst the Mann-Whitney U-test was used to compare non-normally distributed numeric variables with normality assessed using the Shapiro-Wilk test; a $P$ value of $< 0.05$ was considered significant. Analyses were performed with StataMP v15.0 (StataCorp, College Station, TX, USA).

3 | RESULTS

We identified 116 out-patients prescribed rifampicin without concurrent isoniazid by the department of liver medicine between 2012 and 2016 inclusive (Figure 1). Of these, four (2.4%) prescriptions were not made for the treatment pruritus and seven (6.0%) prescriptions were never commenced. 105 patients were therefore included in the final analysis.

One thousand three hundred and eighteen patients were prescribed rifampicin without isoniazid by departments other than liver medicine over the same time period. To assess whether these patients had received rifampicin for pruritus, 116 records were randomly selected. None had received rifampicin for pruritus: 45 (38.8%) received rifampicin for skin and wound infections; 22 (19.0%) for mycobacterium tuberculosis infections; 17 (14.7%) for bone or joint infections; 17 (14.7%) as anti-microbial prophylaxis; 8 (6.9%) for nontuberculosis mycobacterial infections; and 7 (6.0%) for other reasons.

FIGURE 1 Patient selection. Patient cohort selection and exclusions from all patients prescribed rifampicin without isoniazid by the department of liver medicine from 2012 to 2016 inclusive.
other infections. Based on the absence of prescriptions of rifampicin for pruritus by departments other than liver medicine, only prescriptions by the department of liver medicine were further evaluated.

The characteristics of the patient cohort are recorded as Table 1. Of the 105 patients analysed, 94 (89.5%) were already prescribed medications other than rifampicin at the point of rifampicin prescription, with a median of 5 (IQR 3-6) nonrifampicin medications. Major concurrent medications were 66 (62.9%) taking ursodeoxycholic acid, 33 (31.4%) proton pump inhibitors, 26 (24.8%) cholestyramine, 22 (21.0%) nonrifampicin antibiotics, 21 (20.0%) 5-aminosalicylic acid preparations, 15 (14.3%) anti-histamines, 9 (8.6%) azathioprine or 6-mercaptopurine, 10 (9.5%) prednisolone and 8 (7.6%) statins. Two (1.9%) patients were prescribed concurrent sertraline and one patient (1.0%) was prescribed naltrexone.

At baseline, many patients had significantly deranged liver biochemistry (Table 1). 44 (41.9%) patients had a baseline bilirubin ≥ 2 × ULN, 23 (21.9%) patients had a baseline bilirubin ≥ 100 µmol/L (≥ 5.8 mg/dL), and 11 (10.5%) had a baseline ALT > 5 × ULN with 28 (26.7%) > 3 × ULN.

Of the 105 patients followed up for a median of 131 days (IQR 52-295) taking rifampicin, 5 (4.8%) patients diagnosed with hepatitis consistent with rifampicin-induced hepatitis with a RUCAM score ≥ 6 (Figure 2; Table 2). The median time to diagnosis of rifampicin-induced hepatitis was 70 days (range 27-130). There were no significant differences in baseline characteristics between patients who were diagnosed with rifampicin-induced hepatitis and those that were not (Table 1). One further patient was diagnosed with rifampicin-associated acute kidney injury without associated hepatitis.

During our median follow-up of 809 days, we identified 29 patients who met biochemical criteria for potential DILI. Of these, 21 had undergone liver transplantation immediately prior to the derangement in liver biochemistry and were not further analysed. Of the remaining 8, 5 represented rifampicin-related DILI as assessed by RUCAM and are described in Table 2. Three patients’ derangements in liver biochemistry were scored as not related to rifampicin. One patient reached biochemical criteria at 451 days following rifampicin initiation with a RUCAM score of −2 and a clinical course involving excess alcohol consumption; one at 545 days with a RUCAM score of −2 and a clinical diagnosis of deteriorating PSC; and one at 1239 days with a RUCAM score of −1 and with a clinical course that involved an undiagnosed febrile illness associated with cerebrospinal fluid lymphocytosis.

During the first 120 days of follow-up, we assessed for milder fluctuations in liver biochemistry. Serum ALT activity rose to ≥2 × baseline and ≥2 × ULN in 6 (6.0%) of 101 patients not considered to have developed rifampicin induced liver injury (range 2.1-3.8 fold rise). For serum bilirubin, 5 of 101 (5.0%) patients developed elevations to ≥2 × baseline and ≥2 × ULN without concurrent significant elevations in serum ALT activity (range 2.3-3.0 fold rise).

Other than the 6 patients who developed major adverse effects, 17 (16.2%) patients reported resolution of pruritus and stopped taking rifampicin, 9 (8.6%) reported a lack of efficacy despite dose uptitration, 13 patients (12.4%) reported intolerance (1 abdominal discomfort, 1 discolouration of bodily secretions, 5 gastro-intestinal disturbance, 1 localised perineal skin reaction, 1 lethargy and 4

| Variable | Hepatitis (5) | No hepatitis (100) | P |
|----------|--------------|--------------------|---|
| Gender (n) |              |                    |   |
| Female | 3 (60.0%) | 62 (62.0%) | 1.000 |
| Male | 2 (40%) | 38 (38.0%) |               |
| Age (years + IQR) | 37 (28-43) | 44 (32-59) | 0.257 |
| BMI (kg/m² + IQR) | 25.6 (25.5-25.9) | 24.3 (21.8-27.1) | 0.309 |
| Nonrifampicin medications (n + IQR) | 5 (3-6) | 4 (3-6) | 0.294 |
| Starting rifampicin dose (mg/d) | | |
| 150 | 0 (0.0%) | 19 (19.0%) | 0.479 |
| 300 | 5 (100%) | 77 (77.0%) |               |
| 600 | 0 (0.0%) | 4 (4.0%) |               |
| Baseline laboratory values | | |
| ALT (IU/mL + IQR) | 86 (85-95) | 77 (41-152) | 0.500 |
| AST (IU/mL + IQR) | 123 (72-191) | 85 (23-131) | 0.300 |
| Bili (µmol/L + IQR) | 29 (17-99) | 36 (14-87) | 0.630 |
| ALP (IU/mL + IQR) | 399 (272-414) | 396 (221-674) | 0.690 |
| Alb (g/dL + IQR) | 41 (41-44) | 42 (36-45) | 0.880 |
| Primary liver diagnosis (n) | | |
| PSC | 1 (20.0%) | 43 (43.0%) | [1] 0.900 |
| PBC | 3 (60.0%) | 33 (33.0%) | [3]               |
| Congenital | — | 4 (4.0%) |               |
| DILI | 1 (20.0%) | 3 (3.0%) |               |
| Ischaemic cholangiopathy | — | 3 (3.0%) | [1]               |
| Other | — | 3 (3.0%) |               |
| ALD | — | 2 (2.0%) | [1]               |
| IgG4 | — | 2 (2.0%) | [1]               |
| SSC | — | 2 (2.0%) |               |
| Transporter deficiencies | — | 2 (2.0%) |               |
| Cancer | — | 1 (1.0%) |               |
| Hepatitis C | — | 1 (1.0%) |               |
| ICP | — | 1 (1.0%) |               |
| Documented alcohol excess (n) | 1 (20.0%) | 3 (3.0%) | 0.053 |
| HBsAg + (n) | — | — |               |
| HCVAb + (n) | — | 2 (2.0%) | —               |

Numbers in square brackets denote the number of patients who had previously undergone liver transplantation; P values are calculated by the Mann–Whitney U-test or χ² test as appropriate.

BMI, body mass index; ALT, alanine aminotransferase; AST, aspartate aminotransferase; Bili, serum bilirubin; ALP, alkaline phosphatase; Alb, albumin; PSC, primary sclerosing cholangitis; PBC, primary biliary cholangitis; DILI, drug-induced liver injury; ALD, alcohol-induced liver disease; IgG4, IgG4-related disease; SSC, secondary sclerosing cholangitis; ICP, intrahepatic cholestasis of pregnancy.
without a recorded reason). 21 (20.0%) received liver transplants, 3 (2.9%) were transferred to palliative care, 2 (1.9%) died, 5 (4.8%) stopped taking rifampicin for unrecorded reasons, and 29 (27.6%) continued to take rifampicin over the time period studied. Figure 3 details the proportion of patients who remained free of major adverse events, minor adverse events and who continued to take rifampicin.

During treatment, 21 (20.0%) of patients received an uptitration in their dosage of rifampicin. Two of the five patients who developed rifampicin-induced hepatitis received an uptitration in rifampicin dosage prior to developing hepatitis.

Of those five patients who developed rifampicin-induced hepatitis, liver biochemistry resolved to baseline after cessation of rifampicin in four (80%). One patient who was treated with rifampicin for pruritus associated with primary biliary cholangitis was admitted, underwent a liver biopsy which showed bridging fibrosis with a patchy predominantly mononuclear infiltrate containing both lymphocytes and plasma cells, some interface hepatitis and marked-and in places confluent-parenchymal hepatocellular necrosis. She was treated with corticosteroids with subsequent resolution of liver biochemistry to baseline. The one patient with acute kidney injury recovered to baseline renal function after cessation of rifampicin.

4 | DISCUSSION

Here, we present the largest, real-world, cohort of patients treated with rifampicin for pruritus in liver disease published to date. Within our mixed aetiology cohort, we demonstrate that 95% of patients did not have any concern for hepatotoxicity, but that in 5% a rifampicin-induced hepatitis was diagnosed. This finding is in contrast with the literature from controlled trials of rifampicin for pruritus where no cases of hepatitis were reported, but is consistent with isolated case reports and the literature derived from tuberculosis therapy. Our hepatitis rate of 4.8% is higher than the median of 1.1% reported for tuberculosis treatment regimens not containing isoniazid by one meta-analysis, but is within the range of rates reported for tuberculosis patients treated with both isoniazid and rifampicin, and less than reported rates of 10%-20% for any increase in serum transaminase activity reported with rifampicin therapy.

Attributing liver injury to a given potential causative agent is challenging. In this study we used the established RUCAM, which has been widely used in other studies and has the benefit of being points-based rather than explicitly relying on individual opinion. However, it is important to note that recent commentary and guidelines have also emphasised the value of expert opinion in diagnosing DILI. Furthermore, the RUCAM has been suggested to potentially underestimate the rate of drug-induced liver injury and to demonstrate more inter-assessor variability than other methodology. In this study, we used a variation on the original RUCAM to account for deranged baseline liver biochemistry. Although such an adjustment is consistent with that promoted by a body expert opinion, it represents a variation from the initial RUCAM specification and is therefore likely to have differing sensitivity and specificity for diagnosing DILI.

Although the number of patients who developed rifampicin-induced hepatitis in our cohort is small and our analysis is retrospective, there were no statistically significant distinguishing features that predicted subsequent development of hepatitis; a much larger cohort would, however, be necessary to investigate risk factors more conclusively. This is in contrast with the work on those treated for mycobacterial infection with rifampicin, where alcohol excess, low BMI, low serum albumin, age and gender have been suggested as predisposing factors. Multi-centre studies will be needed to further investigate potential risk factors for rifampicin-induced hepatitis in the context of liver disease.
Our cohort included some 23 patients with a baseline serum bilirubin of over 100 μmol/L (≥ 5.8 mg/dL). The UK package insert of rifampicin states that its use is contra-indicated in jaundice, although anecdotally many liver clinicians will consider using rifampicin for the treatment of pruritus despite jaundice.25 We note, however, that it is our practice to co-prescribe oral vitamin K for icteric patients receiving rifampicin to reduce the risk of coagulopathy.26 None of our markedly jaundiced patients developed hepatitis and we note that a separately reported group of markedly jaundiced patients with hepatocellular secretory failure predominantly attributed to biliary transporters dysfunction are reported as having safely received rifampicin for up to 10 weeks.27 Of our cohort, although one patient required corticosteroids and admission to hospital, none of our 105 patients developed life-threatening complications from rifampicin despite some having advanced liver disease at baseline. Given that there was no established protocol for the monitoring of liver biochemistry during the time period assessed, it is possible that some further sub-clinical rifampicin-induced hepatitis may have escaped diagnosis. Nevertheless, our results suggest that rifampicin therapy is relatively safe in cholestatic jaundice.

Liver patients with cholestatic disorders may be prescribed multiple therapeutic compounds and our cohort was taking a median of 5 nonrifampicin medications. Although this number did not vary between groups that did and did not develop rifampicin-associated hepatitis, we cannot exclude the potential for drug-drug interactions promoting hepatitis, especially considering that over 20% of our patients were taking long-term antibiotics, predominantly as prophylaxis against recurrent cholangitis. A further variable that cannot be

### TABLE 2  Liver biochemistry at baseline and at diagnosis of rifampicin induced hepatitis

| Patient | 1 | 2 | 3b | 4 | 5c |
|---------|---|---|----|---|----|
| Major diagnosis | PBC | PSC | PBC | DILI | PBC |
| Age (y) | 55 | 28 | 37 | 26 | 43 |
| Gender (M/F) | M | M | F | F | F |
| Nonrifampicin prescriptions | 6 | 3 | 6 | 3 | 4 |
| RUCAM score | 8 | 7 | 11 | 8 | 6 |

| Variable | Normal range | Units | Laboratory values at baseline | Laboratory values at diagnosis |
|----------|---------------|-------|--------------------------------|--------------------------------|
| Bili | <22 | (μmol/L) | 99 | 17 | 15 | 348 | 29 |
| ALP | 35-105 (F)/40-130 (M) | (IU/L) | 652 | 399 | 178 | 414 | 272 |
| AST | 5-43 | (IU/L) | 168 | — | 65 | 78 | 213 |
| ALT | 5-41 | (IU/L) | 85 | 95 | 41 | 86 | 221 |
| Alb | 34-51 | (g/L) | 37 | 41 | 44 | 41 | 45 |
| Cr | 50-111 | (μmol/L) | 71 | 71 | 63 | 61 | 59 |
| eGFR | — | (mL/min) | >90 | >90 | >90 | >90 |
| INR | 0.8-1.2 | — | 1.0 | 0.9 | 1.1 | 1.0 | 1.0 |
| Eosinophils | <0.4 | ×10⁹/L | 0.1 | 0.2 | 0.2 | 0.1 | 0.1 |
| Time until diagnosisa | — | (d) | 97 | 130 | 70 (14) | 27 (20) | 70 |
| Bili | <22 | (μmol/L) | 201 | 39 | 126 | 72 | 186 |
| ALP | 35-105 (F)/40-130 (M) | (IU/L) | 360 | 851 | 227 | 200 | 176 |
| AST | 5-43 | (IU/L) | 286 | — | 646 | 158 | — |
| ALT | 5-41 | (IU/L) | 186 | 557 | 492 | 310 | 1050 |
| Alb | 34-51 | (g/L) | 34 | 39 | 43 | 44 | 33 |
| Cr | 50-111 | (μmol/L) | 78 | 58 | 76 | 57 | 61 |
| eGFR | — | (mL/min) | 90 | >90 | 74 | >90 | >90 |
| INR | 0.8-1.2 | — | 1.7 | 1.1 | 1.3 | 1.0 | 1.9 |
| Eosinophils | <0.4 | ×10⁹/L | 0.1 | 0.2 | 0.3 | 0.2 | 0.1 |

RUCAM, Roussel-Uclaf causality assessment method score where ≥ 6 represents probable drug (rifampicin)-induced hepatitis; PBC, primary biliary cholangitis; PSC, primary sclerosing cholangitis; DILI, (cholestatic) drug-induced liver injury. Bili, serum bilirubin (μmol/L); ALP, alkaline phosphatase (IU/mL); AST, aspartate aminotransferase (IU/mL); ALT, alanine aminotransferase (IU/mL); Alb, serum albumin (g/L); Cr, serum creatinine (μmol/L); INR, international normalised ratio.

aDays from prescription to diagnosis, numbers in brackets indicate time from dose uptitration.
bPatient received a re-challenge with rifampicin after resolution of initial hepatitis which again provoked significant elevations in serum transaminase activity.
cPatient admitted for treatment with corticosteroids.
accounted for within the sample size of this mixed aetiology cohort is interactions between rifampicin prescription and subtype of underlying cholestatic liver disease.

The median time to onset of hepatitis in our cohort was 70 days from initiation of rifampicin therapy. Most of the patients were followed up for longer than this period with the majority finding rifampicin tolerable and effective. Notably our median time of 70 days until onset of hepatitis is longer than the reported median interval to the development of hepatitis in cohorts of tuberculosis patients of approximately 15 to 30 days. Importantly, two of our patients developed hepatitis after the end of the period of biochemical monitoring suggested by recent guidelines. We note that two of the three cases of rifampicin-induced hepatitis reported by Prince et al occurred at 11 and 14 months after drug initiation. Again, given the absence of protocol liver biochemical monitoring and the retrospective nature of this study, it is possible that the number of cases of rifampicin-induced hepatitis described here is an underestimate with cases meeting our criteria potentially being missed.

Our study provides real-world experience of the use of rifampicin in cholestatic pruritus. We demonstrate useful reference data for clinicians who should counsel patients carefully: reassuringly 95% of our patients did not develop any liver injury, and the 5% that did develop hepatitis all recovered after drug cessation with only one patient requiring further intervention. Many patients with marked jaundice and advanced liver disease took rifampicin safely. In the absence of alternative safe, licensed and equally effective agents, clinicians may consider, the use of rifampicin in cholestatic pruritus.

ACKNOWLEDGEMENTS

GJW and GMH are supported by the National Institute for Health Research Birmingham Biomedical Research Unit; GMH receives further support from the UK Medical Research Council funded UK-PBC stratified medicine platform (www.uk-pbc.com), an EU Career Development Award and is also Chief Investigator for UK-PSC (www.uk-psc.com), a NIHR Translational Research Collaboration. GJW has benefitted from a UK Medical Research Council Clinical Research Fellowship. The funders had no direct role in the conduct or reporting of this study.

Declaration of personal interests: None.

AUTHORSHIP

Guarantor of the article: Gwilym J Webb.

Author contributions: GJW, CL and GMH conceived the study. GJW and SRR collected the data. All authors then contributed to data analysis and drafting the manuscript.

ORCID

G. J. Webb http://orcid.org/0000-0002-0710-5644

REFERENCES

1. Bergasa NV. The pruritus of cholestasis. J Hepatol. 2005;43:1078-1088.
2. Bachs L, Parés A, Elena M, et al. Comparison of rifampicin with phenobarbitone for treatment of pruritus in biliary cirrhosis. Lancet. 1989;1:574-576.
3. Podesta A, Lopez A, Terg R, et al. Treatment of pruritus of primary biliary cirrhosis with rifampin. Dig Dis Sci. 1991;36:216-220.
4. Ghent CN, Carruthers SG. Treatment of pruritus in primary biliary cirrhosis with rifampin. Results of a double-blind, crossover, randomized trial. Gastroenterology. 1989;94:488-493.
5. Cynamon HA, Andres JM, Iafrate RP. Rifampin relieves pruritus in children with cholestatic liver disease. Gastroenterology. 1990;98:1013-1016.
6. Woolf GM, Reynolds TB. Failure of rifampin to relieve pruritus in chronic liver disease. J Clin Gastroenterol. 1990;12:174-177.
7. Lindor KD, Gershwin ME, Poupon R, et al. Primary biliary cirrhosis. Hepatology. 2009;50:291-308.
8. Hirschfield GM, Beuers U, Corpechot C, et al. EASL Clinical Practice Guidelines: the diagnosis and management of patients with primary biliary cholangitis. J Hepatol. 2017;67:145-172.
9. Saukkonen JJ, Cohn DL, Jasmer RM, et al. An official ATS statement: hepatotoxicity of antituberculosis therapy. Am J Respir Crit Care Med. 2006;174:935-952.
10. Dossing M, Wilcke JT, Askgaard DS, et al. Liver injury during antituberculosis treatment: an 11-year study. Tuber Lung Dis. 1996;77:335-340.
11. Steele MA, Burk RF, DesPrez RM. Toxic hepatitis with isoniazid and rifampin. A meta-analysis. Chest. 1991;99:465-471.
12. Sharma SK, Balamurugan A, Saha PK, et al. Evaluation of clinical and immunogenetic risk factors for the development of hepatotoxicity during antituberculosis treatment. Am J Respir Crit Care Med. 2002;166:916-919.
13. Khurana S, Singh P. Rifampin is safe for treatment of pruritus due to chronic cholestasis: a meta-analysis of prospective randomized-controlled trials. Liver Int. 2006;26:943-948.
14. Tandon P, Rowe BH, Vandermeer B, et al. The efficacy and safety of bile acid binding agents, opioid antagonists, or rifampin in the treatment of cholestasis-associated pruritus. Am J Gastroenterol. 2007;102:1528-1536.
15. Prince MI, Burt AD, Jones DE. Hepatitis and liver dysfunction with rifampicin therapy for pruritus in primary biliary cirrhosis. Gut. 2002;50:436-439.
16. Bachs L, París A, Elena M, et al. Effects of long-term rifampicin administration in primary biliary cirrhosis. Gastroenterology. 1992;102:2077-2080.
17. Alithal GP, Watkins PB, Andrade RJ, et al. Case definition and phenotype standardization in drug-induced liver injury. Clin Pharmacol Ther. 2011;89:806-815.
18. Danan G, Benichou C. Causality assessment of adverse reactions to drugs—1. A novel method based on the conclusions of international consensus meetings: application to drug-induced liver injuries. J Clin Epidemiol. 1993;46:1323-1330.
19. LiverTox. Rifampin. 2014. Available from: https://livertox.nlm.nih.gov/Rifampin.htm. Accessed July 14, 2017.
20. Chalasani NP, Hayashi PH, Bonkovsky HL, et al. ACG Clinical Guideline: the diagnosis and management of idiosyncratic drug-induced liver injury. Am J Gastroenterol. 2014;109:950-66; quiz 967.
21. Lewis JH. Causality assessment: which is best—expert opinion or RUCAM? Clin Liver Dis. 2014;4:4-8.
22. Rockey DC, Seeff LB, Rochon J, et al. Causality assessment in drug-induced liver injury using a structured expert opinion process: comparison to the Roussel-Uclaf causality assessment method. Hepatology. 2010;51:2117-2126.
23. Gronhagen-Riska C, Hellstrom PE, Froseth B. Predisposing factors in hepatitis induced by isoniazid-rifampin treatment of tuberculosis. Am Rev Respir Dis. 1978;118:461-466.
24. Makhlouf HA, Helmy A, Fawzy E, et al. A prospective study of antituberculous drug-induced hepatotoxicity in an area endemic for liver diseases. Hepatol Int. 2008;2:353-360.
25. Datapharm Communications Limited. eMedicines.org.uk. SPC Rifadin 150mg Capsules. 2017. Available from: http://www.medicines.org.uk/emc/medicine/21221. Accessed May 2, 2017.
26. Sampaziotis F, Griffiths WJ. Severe coagulopathy caused by rifampicin in patients with primary sclerosing cholangitis and refractory pruritus. Br J Clin Pharmacol. 2012;73:826-827.
27. Van Dijk R, Kremer AE, Smit W, et al. Characterization and treatment of persistent hepatocellular secretory failure. Liver Int. 2015;35:1478-1488.
28. Rao NK. Hepatotoxicity of antituberculous drugs. J Assoc Physicians India. 1982;30:295-298.

How to cite this article: Webb GJ, Rahman SR, Levy C, Hirschfield GM. Low risk of hepatotoxicity from rifampicin when used for cholestatic pruritus: a cross-disease cohort study. Aliment Pharmacol Ther. 2018;47:1213–1219. https://doi.org/10.1111/apt.14579