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Rifabutin

Updated: June 10, 2018.

OVERVIEW

Introduction

Rifabutin is a rifamycin antibiotic that is similar in structure and activity to rifampin and rifapentine and which is used largely in the prevention of Mycobacterium avium complex (MAC) disease in patients with advanced HIV infection. Rifabutin is associated with transient and asymptomatic elevations in serum aminotransferase and is a likely cause of clinically apparent, acute liver disease.

Background

Rifabutin (rif" a bue' tin) is a rifamycin antibiotic and a synthetic derivative of natural products of the bacterium, Amycolatopsis mediterranei. The rifamycins are complex macrocyclic antibiotics that have activity against several bacteria, but most prominently M. tuberculosis and several atypical mycobacterial species, probably as a result of inhibition of the DNA-dependent RNA polymerase of mycobacteria. These agents are considered bactericidal and are active against both intracellular and extracellular organisms. Rifabutin has similar activity and pharmacokinetics as rifampin, but it is less likely to induce hepatic microsomal, drug metabolizing enzymes and, thus, is an appropriate substitute for rifampin in patients on other medications that would be affected by alteration in the P450 system, such as some antiretroviral agents, benzodiazepines, cyclosporine, macrolide antibiotics, oral contraceptives, and warfarin. Rifabutin is available as 150 mg capsules under the trade name of Mycobutin. The current major indication is for prevention of mycobacterium avium complex (MAC) disease in patients with HIV infection, and treatment of tuberculosis is considered an off-label use. The recommended dose in adults is 300 mg daily in one or two divided doses. Pyridoxine (vitamin B6) is commonly given with rifabutin to prevent neuropathy. Side effects of rifabutin are uncommon, but include rash, fever, flu-like symptoms, gastrointestinal upset and orange discoloration of urine and sweat. Rifabutin has some, but far less activity than rifampin as an inducer of the hepatic microsomal drug metabolizing P450 enzymes (CYP 1A2, 2C9, 2C19 and 3A4), the relative potencies being: rifampin (1.0), rifapentine (0.85), and rifabutin (0.4). Nevertheless, use of other medications (such as birth control pills, beta-blockers, benzodiazepines, cyclosporine and oral anticoagulants) with rifabutin should be carefully considered and monitored. Rare but potentially severe adverse events include uveitis, hypersensitivity reactions and C. difficile diarrhea.

Hepatotoxicity

Because of its limited use, the effects of rifabutin on the liver have been less well defined than those of rifampin, but they are likely to be similar. Thus, studies on the prevention of MAC in HIV infected patients with rifabutin, minor, transient elevations in serum aminotransferase levels occurred in 3% to 8% of patients, but these abnormalities rarely required dose adjustment or discontinuation. Clinically apparent liver injury due to

rifabutin has not been reported, but it is likely to be similar to rifampin in its potential for causing acute liver injury. Because rifabutin is usually given in combination with other agents used to treat HIV infection, the cause of the acute liver injury in patients on rifabutin-containing regimens may be difficult to relate to a single agent. Typically, the onset of injury due to rifampin is within 1 to 6 weeks and the serum enzyme pattern is usually hepatocellular at the onset of injury, but can cholestatic and mixed in contrast to isoniazid and pyrazinamide. Extrahepatic manifestations due to rifampin hepatotoxicity such as fever, rash, arthralgias, edema and eosinophilia are uncommon as is autoantibody formation. This potential for hepatotoxicity has not been demonstrated specifically for rifabutin, and some patients with apparent hepatotoxicity attributed to rifampin have tolerated rifabutin without recurrence of liver injury.

Likelihood score: D (possible rare cause of clinically apparent liver injury).

Mechanism of Injury

The mechanism of rifamycin associated hepatotoxicity is not known, but these agents are extensively metabolized by the liver and induce multiple hepatic enzymes. Thus, the cause of injury is likely to be due to idiosyncratic metabolic products that are either directly toxic or induce an immunologic reaction.

Outcome and Management

For the rifamycins, the severity of hepatic injury ranges from asymptomatic elevations in serum aminotransferase levels, jaundice without apparent hepatic injury, symptomatic self-limited hepatitis to severe fulminant liver failure and death. In most cases, complete recovery is expected after stopping the drug and is usually rapid and complete. The rifamycins have not been associated with vanishing bile duct syndrome or chronic hepatitis. There is likely to be cross sensitivity to liver injury among the various rifamycins (rifampin, rifabutin, rifapentine), but not with other first or second line antituberculosis agents.

[First line medications used in the therapy of tuberculosis in the US include ethambutol, isoniazid, pyrazinamide, rifabutin, rifampin, and rifapentine. Second line medications include streptomycin, capreomycin, cycloserine, ethionamide, fluoroquinolones such as levofloxacin and moxifloxacin, aminoglycosides such as amikacin, and para-aminosalicylic acid (PAS).] Specific, regularly updated recommendations on therapy of tuberculosis can be found on the Centers for Disease Control and Prevention website: https://www.cdc.gov/tb/topic/treatment/

Drug Class: Antituberculosis Agents

Other Drugs in the Class: Bedaquiline, Capreomycin, Cycloserine, Ethambutol, Ethionamide, Isoniazid, Pyrazinamide, Rifampin, Rifapentine, Streptomycin

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Rifabutin – Mycobutin®

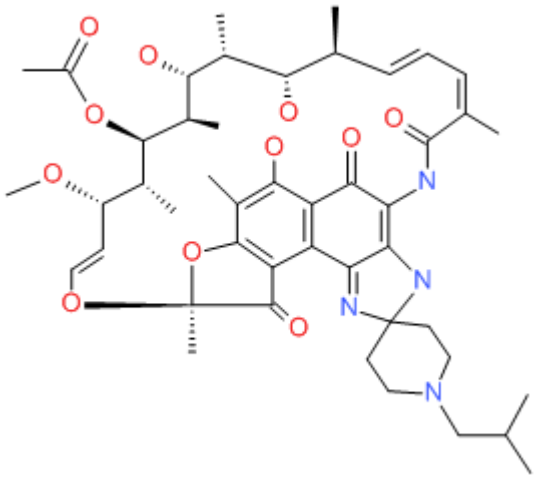
DRUG CLASS

Antituberculosis Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NUMBER	MOLECULAR FORMULA	STRUCTURE
Rifabutin	72559-06-9	C46-H62-N4-O11	

ANNOTATED BIBLIOGRAPHY

References updated: 10 June 2018

Zimmerman HJ. Antituberculosis agents. In, Zimmerman HJ. Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver. 2nd ed. Philadelphia: Lippincott, 1999, pp. 611-21.

(Extensive review of hepatotoxicity of antituberculosis medications including rifampin [but not rifabutin or rifapentine] published in 1999).

Verma S, Kaplowitz N. Hepatotoxicity of antituberculosis drugs. In, Kaplowitz N, DeLeve LD, eds. Drug-induced liver disease. 3rd ed. Amsterdam: Elsevier, 2013, pp. 483-504.

(Review of hepatotoxicity of antituberculosis drugs).

Gumba T. Chemotherapy of tuberculosis, mycobacterium avium complex disease and leprosy. In, Brunton LL, Chabner BA, Knollman BC, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 12th ed. New York: McGraw-Hill, 2011, pp. 1549-70.

(Textbook of pharmacology and therapeutics).

Acocella G, Lamarina F, Tenconi LT, Nicolis FB. Study of the excretion in bile and concentration in the gall bladder wall of rifamide. Gut 1966; 7: 380-6. PubMed PMID: 5917425.

(Rifamide had no effect on bilirubin levels, and high levels found in bile).

Scheuer PJ, Summerfield JA, Lal S, Sherlock S. Rifampicin hepatitis. Lancet 1974; i: 421-5. PubMed PMID: 4131429.

(Analysis of 11 patients with hepatitis due to antituberculosis medications, some attributed to rifampin [none receiving it alone]; onset usually within 3 weeks, several having hepatitis with cholestasis).

Allue X, Sanjurjo P, Fidalgo I, Bilbao F. Hepatic toxicity of antituberculous drugs in children. Helv Paediatr Acta 1976; 31: 381-7. PubMed PMID: 1017983.

(3 cases of jaundice in children ages 8, 9 and 2 years, arising 14, 4 and 25 days after starting antituberculosis therapy with isoniazid and rifampin, two recovering upon withdrawal of rifampin only, one developed jaundice only when rifampin was added and subsequently died).

Pessayre D, Bentata M, Degott C, Nouel O, Miguet JP, Rueff B, Benhamou JP. Isoniazid-rifampin fulminant hepatitis. A possible consequence of the enhancement of isoniazid hepatotoxicity by enzyme induction. Gastroenterology 1977; 72: 284-9. PubMed PMID: 830577.

(6 cases of fulminant hepatitis attributed to rifampin-isoniazid combination, ages 15 to 67 years, onset 6-10 days after starting INH and rifampin, all had encephalopathy, peak bilirubin 2.4-13.6 mg/dL, ALT 26-80 times ULN, protime 18-36%, without fever, rash, eosinophilia or autoantibodies, rapid onset, recovery in all).

Taillan B, Chichmanian RM, Fuzibet JG, Vinti H, Taillan F, Dellamonica P, Dujardin P. [Jaundice caused by rifampicin: 3 cases] Rev Med Interne 1989; 10: 409-11. PubMed PMID: 2488482.

(3 elderly women developed jaundice [2-8x ULN] within 6-7 days of starting rifampin with normal ALT, Alk P 2-3 times ULN, resolution in 14-30 days; in one biopsy showed "centrolobular cholestasis").

Chiu J, Nussbaum J, Bozzette S, Tilles JG, Young LS, Leedom J, Heseltine PN, et al. and California Collaborative Treatment Group. Treatment of disseminated Mycobacterium avium complex infection in AIDS with amikacin, ethambutol, rifampin, and ciprofloxacin. Ann Intern Med 1990; 113: 358-61. PubMed PMID: 2382918.

(17 patients with AIDs and MAC infection were treated with amikacin for 4 weeks and then 12 weeks of ciprofloxacin, ethambutol and rifampin; therapy stopped early in 2 patients for hepatitis, but no details given).

Mancini P, Pasqua F, Mazzei L, Olliaro P. Rifabutin treatment for tuberculosis patients with liver function abnormalities. J Antimicrob Chemother 1992; 30: 242. PubMed PMID: 1328137.

(Among 7 patients who developed enzyme elevations during combination therapy [isoniazid, rifampin and ethambutol] of tuberculosis, none had recurrence of ALT or AST elevations when re-treated using the same drugs, except for rifabutin instead of rifampin).

Gonzalez-Montaner LJ, Natal S, Yongchaiyud P, Olliaro P. Rifabutin for the treatment of newly-diagnosed pulmonary tuberculosis: a multinational, randomized, comparative study versus Rifampicin. Rifabutin Study Group. Tuber Lung Dis 1994; 75: 341-7. PubMed PMID: 7841427.

(Among 520 pateints with tuberculosis treated with a 4 drug regimen of isoniazid, ethambutol and pyrazinamide combined with either rifampin or one of 2 doses of rifabutin for 6 months and followed for 2 years, efficacy was similar among the 3 groups and adverse events were highest with the higher rifabutin dose, but "there was no obvious treatment effect on liver or kidney function").

Griffith DE, Brown BA, Girard WM, Wallace RJ Jr. Adverse events associated with high-dose rifabutin in macrolide-containing regimens for the treatment of Mycobacterium avium complex lung disease. Clin Infect Dis 1995; 21: 594-8. PubMed PMID: 8527549.

(Open label study of rifabutin in 24 patients with MAC; side effects were common and 3 [12%] had liver test abnormalities, one requiring dose modification who had a recurrence on reexposure).

Schwander S, Rüsch-Gerdes S, Mateega A, Lutalo T, Tugume S, Kityo C, Rubaramira R, et al. A pilot study of antituberculosis combinations comparing rifabutin with rifampicin in the treatment of HIV-1 associated tuberculosis. A single-blind randomized evaluation in Ugandan patients with HIV-1 infection and pulmonary tuberculosis. Tuber Lung Dis 1995; 76: 210-8. PubMed PMID: 7548903.

(Controlled trial of rifabutin vs rifampin in combination with isoniazid, ethambutol and pyrazinamide in 50 patients with HIV and tuberculosis; no clinically apparent liver injury or jaundice; rates of ALT elevations not given).

Dautzenberg B, Olliaro P, Ruf B, Esposito R, Opravil M, Hoy JF, Rozenbaum W, et al. Rifabutin versus placebo in combination with three drugs in the treatment of nontuberculous mycobacterial infection in patients with AIDS. Clin Infect Dis 1996; 22: 705-8. PubMed PMID: 8729209.

(Rifabutin used in 102 patients with MAC in European trials; no information on hepatotoxicity).

Havlir DV, Dubé MP, Sattler FR, Forthal DN, Kemper CA, Dunne MW, Parenti DM, et al. Prophylaxis against disseminated Mycobacterium avium complex with weekly azithromycin, daily rifabutin, or both. California Collaborative Treatment Group. N Engl J Med 1996; 335: 392-8. PubMed PMID: 8676932.

(Controlled trial of azithromycin vs rifabutin vs both for prevention of MAC disease in 693 HIV infected patients; 1-2% of subjects developed laboratory abnormalities requiring discontinuation, a proportion being ALT elevations).

Benator D, Bhattacharya M, Bozeman L, Burman W, Cantazaro A, Chaisson R, Gordin F, et al; Tuberculosis Trials Consortium. Rifapentine and isoniazid once a week versus rifampicin and isoniazid twice a week for treatment of drug-susceptible pulmonary tuberculosis in HIV-negative patients: a randomised clinical trial. Lancet 2002 17; 360: 528-34. PubMed PMID: 12241657.

(Among 1004 patients treated with either rifapentine [once weekly] or rifampin [twice weekly] with isoniazid, ALT elevations >5 times ULN occurred in 2.6% on rifapentine and 3.5% on rifampin; no deaths due to liver injury).

American Thoracic Society; Centers for Disease Control and Prevention (CDC); Infectious Diseases Society of America. Treatment of tuberculosis. MMWR Recomm Rep 2003; 52 (RR-11): 1-77. PubMed PMID: 12836625.

(Detailed recommendations on therapy of tuberculosis including drug regimens [including rifabutin and rifapentine], side effects, monitoring and optimal approaches to follow up).

Reichman LB, Lardizabal A, Hayden CH. Considering the role of four months of rifampin in the treatment of latent tuberculosis infection. Am J Respir Crit Care Med 2004; 170: 832-5. PubMed PMID: 15297274.

(Review of the safety and efficacy of a 4 month course of rifampin monotherapy for treatment of latent tuberculosis).

Marschall HU, Wagner M, Zollner G, Fickert P, Diczfalusy U, Gumhold J, Silbert D, et al. Complementary stimulation of hepatobiliary transport and detoxification systems by rifampicin and ursodeoxycholic acid in humans. Gastroenterology 2005; 129: 476-85. PubMed PMID: 16083704.

(Gene changes in liver after 1 week of rifampin, ursodiol or placebo in 30 patients undergoing electric cholecystectomy found increase in UGT1A1, CYP 3A4 and ABCC2 [MRP2], with significant decrease in serum bilirubin levels in patients receiving rifampin).

Corpechot C, Ping C, Wendum D, Matsuda F, Barbu V, Poupon R. Identification of a novel 974C-->G nonsense mutation of the MRP2/ABCC2 gene in a patient with Dubin-Johnson syndrome and analysis of the effects of rifampicin and ursodeoxycholic acid on serum bilirubin and bile acids. Am J Gastroenterol 2006; 101: 2427-32. PubMed PMID: 16952291.

(24 year old man with Dubin Johnson syndrome developed jaundice within days of starting rifampin with no change in ALT or Alk P [bilirubin 2.2 rising to 6.0 mg/dL, 4.2 mg/dL direct], which resolved on stopping drug; shown to have a mutation in ABCC2 [MRP2]).

Munsiff SS, Kambili C, Ahuja SD. Rifapentine for the treatment of pulmonary tuberculosis. Clin Infect Dis 2006; 43: 1468-75. PubMed PMID: 17083024.

(Review of role of rifapentine, a cyclopentyl substituted semisynthetic rifamycin, similar activity and resistance pattern, but longer half-life allowing for once weekly therapy; efficacy may be slightly less than rifampin and it is recommended only in selected patients; side effects are similar to rifampin).

Schechter M, Zajdenverg R, Falco G, Barnes GL, Faulhaber JC, Coberly JS, Moore RD, et al. Weekly rifapentine/ isoniazid or daily rifampin/ pyrazinamide for latent tuberculosis in household contacts. Am J Respir Crit Care Med 2006; 173: 922-6. PubMed PMID: 16474028.

(In trial comparing rifapentine with isoniazid for 3 months [n=206] vs rifampin and pyrazinamide for 2 months [n=193], hepatotoxicity arose in 10% on pyrazinamide vs 1% on isoniazid combination, all resolved within two months, no hospitalizations or deaths).

Saukkonen JJ, Cohn DL, Jasmer RM, Schenker S, Jereb JA, Nolan CM, Peloquin CA, et al.; ATS (American Thoracic Society) Hepatotoxicity of Antituberculosis Therapy Subcommittee. An official ATS statement: hepatotoxicity of antituberculosis therapy. Am J Respir Crit Care Med 2006; 174: 935-52. PubMed PMID: 17021358.

(American Thoracic Society recommendations regarding hepatotoxicity of antituberculosis therapy; for latent infection, 9 months of isoniazid is first choice and 4 months of rifampin second; clinical monitoring is recommend for all patients and biochemical monitoring for those at high risk and possibly the elderly [ALT values at 1, 3 and 6 months or every 1-2 months]; hold therapy if ALT >5 times ULN or if symptoms are present and ALT >3 times ULN; mentions that hepatotoxicity due to rifabutin is uncommon and ALT elevations >3 times ULN were reported in 3-8% of patients receiving rifabutin for MAC prophylaxis).

Centers for Disease Control and Prevention (CDC). Trends in tuberculosis—United States, 2008. MMWR Morb Mortal Wkly Rep 2009; 58: 249-53. PubMed PMID: 19300406.

(In 2008, 12,898 cases of active tuberculosis were reported in US, lowest rate since reporting began in 1953; incidence rate=3/100,000; 1.2% with multidrug-resistant strains).

Gao XF, Li J, Yang ZW, Li YP. Rifapentine vs. rifampicin for the treatment of pulmonary tuberculosis: a systematic review. Int J Tuberc Lung Dis 2009; 13: 810-9. PubMed PMID: 19555529.

(Systematic review of randomized controlled trials comparing rifapentine to rifampin in combination regimens for tuberculosis found no differences in rates of side effects including hepatotoxicity; no deaths or even hospitalization for liver disease reported in 3 trials involving 644 patients).

Reuben A, Koch DG, Lee WM; Acute Liver Failure Study Group. Drug-induced acute liver failure: results of a U.S. multicenter, prospective study. Hepatology 2010; 52: 2065-76. PubMed PMID: 20949552.

(Among 1198 patients with acute liver failure enrolled in a US prospective study between 1998 and 2007, 133 were attributed to drug induced liver injury and 25 to antituberculosis agents, including 15 to isoniazid alone [ranking first], 6 to isoniazid combined with other agents, 3 to rifampin and pyrazinamide, and 1 to dapsone; but none were attributed to rifabutin, even in combination).

Horne DJ, Spitters C, Narita M. Experience with rifabutin replacing rifampin in the treatment of tuberculosis. Int J Tuberc Lung Dis 2011; 15: 1485-9. PubMed PMID: 22008761.

(Among 30 patients with tuberculosis switched from rifampin to rifabutin because of liver test abnormalities, only two redeveloped liver injury on rifabutin, whereas 6 of 15 who were switched because of rash had a recurrence).

Sterling TR, Villarino ME, Borisov AS, Shang N, Gordin F, Bliven-Sizemore E, Hackman J, et al.; TB Trials Consortium PREVENT TB Study Team. Three months of rifapentine and isoniazid for latent tuberculosis infection. N Engl J Med 2011; 365: 2155-66. PubMed PMID: 22150035.

(7731 subjects with latent tuberculosis at high risk for active disease were treated with either a 3 month course of directly observed once weekly isoniazid and rifapentine [3 mo INH/R] or standard therapy with 9 months of daily isoniazid [9 mo INH]; after 3 years, rates of active tuberculosis were similar [0.19% after 3 mo INH/R and 0.43% after 9 mo INH], whereas hepatotoxicity was less with 3 mo INH/R [0.4%] than 9 mo INH [2.7%]).

Björnsson ES, Bergmann OM, Björnsson HK, Kvaran RB, Olafsson S. Incidence, presentation and outcomes in patients with drug-induced liver injury in the general population of Iceland. Gastroenterology 2013; 144: 1419-25. PubMed PMID: 23419359.

(In a population based study of drug induced liver injury from Iceland, 96 cases were identified over a 2 year period, including 1 attributed to isoniazid, but none to rifampin or other rifamycins).

Chien JY, Chien ST, Huang SY, Yu CJ. Safety of rifabutin replacing rifampicin in the treatment of tuberculosis: a single-centre retrospective cohort study. J Antimicrob Chemother 2014; 69; 790-6. PubMed PMID: 24243988.

(Among 221 patients with tuberculosis who were switched to rifabutin because of rifampin intolerance, 23 were switched for "severe" and 16 for "mild" hepatitis, of whom 2 developed severe hepatitis on rifabutin with a latency of 11 weeks and recover 9-21 days after stopping).

Lan NT, Thu NT, Barrail-Tran A, Duc NH, Lan NN, Laureillard D, Lien TT, et al. Randomised pharmacokinetic trial of rifabutin with lopinavir/ritonavir-antiretroviral therapy in patients with HIV-associated tuberculosis in Vietnam. PLoS One 2014; 9: e84866. PubMed PMID: 24465443.

(Among 33 HIV positive patients with tuberculosis enrolled in a pharmacokinetic study of rifabutin for 12 weeks, 3 developed liver related adverse events including one with acute hepatitis "followed by death").

Hernández N, Bessone F, Sánchez A, di Pace M, Brahm J, Zapata R, A Chirino R, et al. Profile of idiosyncratic drug induced liver injury in Latin America. An analysis of published reports. Ann Hepatol 2014; 13: 231-9. PubMed PMID: 24552865.

(Systematic review of literature of drug induced liver injury in Latin American countries published from 1996 to 2012 identified 176 cases, 6 of which were attributed to isoniazid, 1 to pyrizamide and 1 to rifampin, but none to rifabutin).

Chalasani N, Bonkovsky HL, Fontana R, Lee W, Stolz A, Talwalkar J, Reddy KR, et al.; United States Drug Induced Liver Injury Network. Features and outcomes of 899 patients with drug-induced liver injury: the DILIN prospective study. Gastroenterology 2015; 148: 1340-52.e7. PubMed PMID: 25754159.

(Among 899 cases of drug induced liver injury enrolled in a US prospective study between 2004 and 2013, 408 were attributed to antimicrobial agents including 54 to antituberculosis agents, mostly due to isoniazid [n=48], only two to rifampin and none to rifabutin).

Puri P, Kaur N, Pathania S, Kumar S, Sharma PK, Sashindran VK. Antitubercular therapy induced liver function tests abnormalities in human immunodeficiency virus infected individuals. Med J Armed Forces India 2017; 73: 12-7. PubMed PMID: 28123239.

(Among 100 patients with HIV infection and tuberculosis, 99 developed liver test abnormalities on antituberculosis therapy, but elevations of ALT or AST above 5 times ULN was more common in patients and antiretroviral therapy [18% vs 3%] and in those with preexisting enzyme elevations).