Drugs 1998 Oct; 56 (4): 607-616
0012-6667/98/0010-0607/$10.00/0

Rifapentine

Blair Jarvis and *Harriet M. Lamb*

Adis International Limited, Auckland, New Zealand

Contents

Abstract

▲ Rifapentine is a rifamycin antibiotic with antimycobacterial activity.

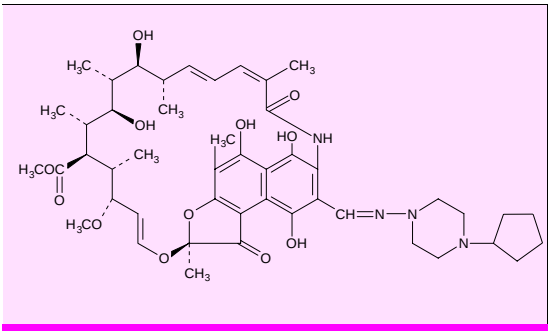
▲ Rifapentine is generally more active against *Mycobacterium tuberculosis* than rifampicin (rifampin), although strains resistant to rifampicin are usually cross-resistant to rifapentine.

▲ Sputum culture conversion rates were slightly higher after 6 months of rifapentine- versus rifampicin-based therapy in patients with pulmonary tuberculosis in a Western study; however, relapse rates were higher in rifapentine recipients during follow-up. The excess relapses in the rifapentine group appeared to be related to poor compliance with non-rifamycin antituberculosis drugs during the intensive phase (first 2 months) of therapy.

▲ Rifapentine- and rifampicin-containing regimens produced similar sputum culture conversion rates with low rates of relapse in 2 randomised clinical trials in patients with smear-positive tuberculosis in China. In one trial, there was no difference in sputum culture conversion rates in patients treated with rifapentine once weekly or rifampicin twice weekly in combination with isoniazid and ethambutol during the continuation phase of treatment.

▲ Hyperuricaemia, which was reported only during the intensive phase, elevated ALT and AST levels and neutropenia were the most common treatment-related adverse events reported in patients receiving rifapentine- or rifampicin-containing regimens for tuberculosis in 1 Western study.

Features and properties of rifapentine (cyclopentylrifamycin)	
Indications	
Pulmonary tuberculosis	Approved in the US Used in China
Mechanism of action	
Antimycobacterial agent	RNA synthesis inhibitor
Dosage and administration	
Usual dose	600mg
Route of administration	Oral
Frequency of administration	
Intensive phase Continuation phase	Twice weekly Once weekly
Pharmacokinetic profile	
Peak plasma concentration	15.1 mg/L
Time to peak plasma concentration	4.8 to 6.6h
Area under the plasma concentration-time curve	319 mg/L • h
Bioavailability	Increased 55% with food
Elimination half-life	13.2h
Adverse events	
Most frequent in combination regimens	Hyperuricaemia, elevated ALT and AST levels, neutropenia



Rifapentine

Rifapentine (cyclopentylrifamycin) is a new oral rifamycin derivative with antimycobacterial activity. The drug is available as 2 distinct formulations: a tablet formulation (Priftin®, DL473, MDL473) approved for the treatment of pulmonary tuberculosis in the US, and a capsule formulation used in the People's Republic of China. The summary of preclinical and pharmacokinetic data is a compilation from both formulations. Clinical data are, however, presented separately as there are significant differences in bioavailability between the 2 formulations.

Rifapentine has a broad spectrum of antimicrobial activity. In addition to its antitubercular activity, the drug is generally more active than rifampicin (rifampin) and less active than rifabutin against strains of *Mycobacterium avium* complex[1-3] and also has activity against Gram-positive and Gram-negative bacteria[4-9] and *Toxoplasma gondii*,[10] but these data will not be reviewed further.

1. Antitubercular Activity

Mechanism of Action

• Rifapentine inhibits bacterial RNA synthesis by binding to the β-subunit of DNA-dependent RNA polymerase in susceptible species.[11] The drug is bactericidal.[11]

In Vitro Activity

In vitro activity is generally measured using the minimum inhibitory concentration (MIC) for a particular strain or the MIC required to inhibit 50% (MIC_{50}) or 90% (MIC_{90}) of strains when population data are available. Some studies also reported the minimum bactericidal concentration (MBC). Susceptibility breakpoints have not been established for rifapentine; arbitrary breakpoints established in individual studies are presented where appropriate.

• *In vitro*, rifapentine is generally more active than rifampicin against sensitive strains of *M. tuberculosis* (fig. 1). MIC values of rifapentine were 2 to 10,[5] 4,[3] and 2.2[12] times lower than, or were similar to,[13] those of rifampicin against clinical isolates of *M. tuberculosis*.

• MBC values of rifapentine (range 0.06 to 0.5 mg/L) were 2-fold lower or similar to those of rifampicin against 4 rifampicin-sensitive strains of *M. tuberculosis*. However, the MBC/MIC ratios for rifapentine were either identical or 4-fold greater than those seen with rifampicin for the same strains.[1]

• In general, rifampicin-resistant strains of *M. tuberculosis* are cross-resistant to rifapentine.[3,12,14] Missense mutations, deletions or insertions within a limited region (*rpoB*) of the β-subunit gene (of DNA-dependent RNA polymerase) of *M. tuberculosis* confer resistance to rifapentine and cross-resistance to rifampicin.[14-16] Consistent with this, only 2 of 555 (0.4%) strains of *M. tuberculosis* differed in their susceptibility to the 2 drugs, and 0 to 8% of rifampicin-resistant strains of *M. tuberculosis* were susceptible to rifapentine.[3,12,13]

Intracellular Activity

• Rifapentine achieves greater intracellular than extracellular concentrations. For example, intracellular concentrations were 27- and 61-fold greater than extracellular concentrations after exposure of human macrophages to rifapentine 10 mg/L *in vitro*.[17,18] Furthermore, rifapentine retained bactericidal activity after passive uptake by human neutrophils[17,19] and macrophages.[17,18]

• The intracellular antimycobacterial activity of rifapentine exceeds that of rifampicin. Intracellular

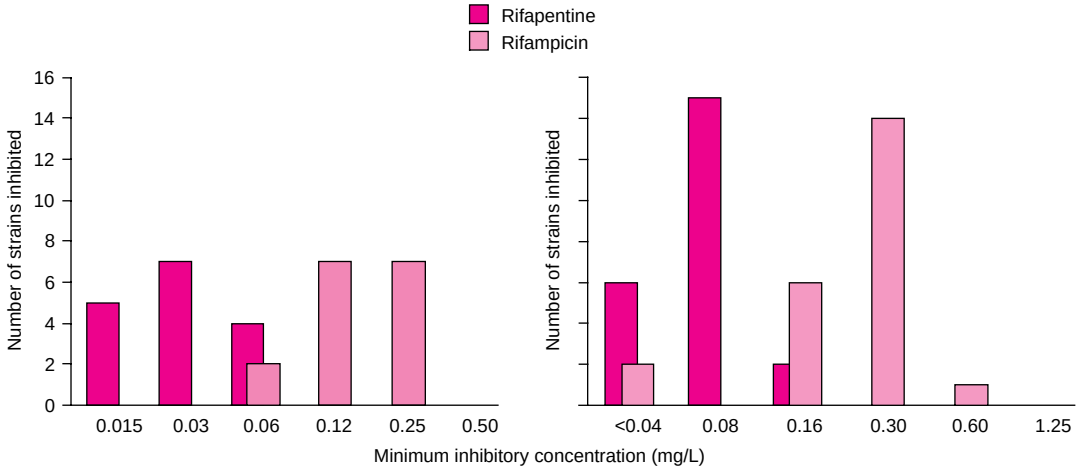


Fig. 1. Comparative *in vitro* activity of rifapentine and rifampicin against rifampicin-sensitive *Mycobacterium tuberculosis*. Strains were obtained from American patients (16 strains) and grown in 7H12 broth at pH 6.8 for 8 days (left)[1] or a mixed patient population (23 strains) and grown on 7H10 medium for 28 days (right).[3] Note that the *x*-axis scales on each graph differ.

MIC and MBC values of rifapentine for 3 strains of *M. tuberculosis* were 2- to 17-fold lower than those of rifampicin in human macrophages.[18]

• *In vitro* exposure of *M. tuberculosis* within human macrophages to declining rifapentine concentrations over 72 hours (similar to plasma concentrations after administration of a 600mg dose in humans) produced a substantial reduction in the mycobacterial population versus that in drug-free, infected control macrophages.[18] In this study, 72-hour exposure to rifapentine resulted in a 2 to 3 $\log_{10}$ decrease in the number of viable mycobacteria within 7 days. Furthermore, when infected cells were exposed to this regimen at weekly intervals for 4 weeks, mycobacterial populations did not rebound. The addition of 25-desacetylrifapentine (the major metabolite of rifapentine) did not enhance the activity of rifapentine in this model.

In Vivo Activity

• In models of overt tuberculosis, *M. tuberculosis* was eradicated from the spleens of mice that received once-weekly rifapentine 16 mg/kg,[20] once-fortnightly rifapentine 10 mg/kg[21] or rifampicin 10 mg/kg 6 days/week for 24 weeks following a 6- or 8-week induction combination regimen (isoniazid 25 mg/kg, rifampicin 10 mg/kg and pyrazinamide 150 mg/kg given 5 or 6 days/week; all drugs were given orally).[20,21] Once-weekly rifapentine 10 mg/kg eradicated all bacteria in one study[21] but was slightly less effective in the other study.[20] Lower doses and less frequent administration of rifapentine were less active in this murine model.[20,21]

• Rifapentine-based combination therapy reduced bacterial counts and prevented the emergence of rifampicin-resistant *M. tuberculosis* in a murine model of tuberculosis.[22] No rifampicin-resistant strains were detected when isoniazid and pyrazinamide were administered once-weekly with rifapentine (at 75 and 300 mg/kg, respectively) or 6 times/week with rifampicin (at 25 and 150 mg/kg/day, respectively).[22] In contrast, once-weekly rifapentine 10 mg/kg or rifampicin 10 mg/kg 6 times/week was associated with the emergence of rifampicin-resistant *M. tuberculosis* in approximately 50% of mice after 8 weeks.[22] However, neither of these regimens, nor several other 8-week rifapentine-based combination regimens, eradicated *M. tuberculosis* from mice.

• Rifapentine has demonstrated efficacy as preventive therapy for tuberculosis in animal models. Oral rifapentine 10 mg/kg 6 days/week for 12 weeks[23] and once weekly for 26 weeks[24] were equally effective in eradicating *M. tuberculosis* from the spleens of immunocompetent mice.

• In an immunocompromised (nude) mouse model of tuberculosis infection, once-weekly oral rifapentine 10 mg/kg and isoniazid 75 mg/kg produced negative organ cultures for *M. tuberculosis* after 26 weeks.[24] The majority of animals relapsed during 12 weeks of follow-up, although mortality rates were low (11%).[24] In contrast, mortality rates exceeded 75% in mice treated with once-weekly rifapentine or daily isoniazid alone for 26 weeks. Furthermore, 13 weeks of treatment with rifapentine and isoniazid (as above) or daily rifampicin 10 mg/kg and pyrazinamide 150 mg/kg failed to protect against death; all animals died during follow-up.[24]

• Oral rifapentine 5 mg/kg/day reduced *M. tuberculosis* counts in lung tissue below the limit of detection in mice infected by a novel low dose aerosol technique that mimics newly diagnosed tuberculosis in humans.[25]

2. Pharmacokinetic Profile

Absorption

• The mean peak plasma concentration (C_{max}) and area under the plasma concentration-time curve from 0 to 72 hours (AUC_{0-72}) were, respectively, 11.8 mg/L and 319 mg/L · h in 20 fasting healthy male volunteers (mean age 25.7 years) after a single 600mg oral dose of rifapentine;[26,27] mean plasma concentrations 24 and 72 hours after administration were 9 and 1 mg/L, respectively.[28] In 14 healthy elderly male volunteers (mean age 71 years) receiving the same dosage, AUC_{0-72} and C_{max} were 41 and 28% higher (AUC_{0-72} 449 mg/L · h, $p < 0.05$ *vs* young volunteers; C_{max} = 15.1 mg/L).[26,27] At steady state, C_{max} was 15.1 mg/L in healthy volunteers (age not stated) receiving 600mg every 72 hours.[29] The time to C_{max} (t_{max}) ranged from 4.8 to 6.6 hours in volunteer studies.[26,27,29]

• Absorption of rifapentine after oral administration is enhanced when the drug is taken after a meal.[20,30-32] The bioavailability was 55% greater[28] and C_{max} and the AUC extrapolated to infinity ($AUC_{0-\infty}$) increased by 44 and 43%, respectively, when a 600mg tablet was administered with food compared with the fasting state.[28,29] In HIV-positive patients (n = 16), the C_{max} and $AUC_{0-\infty}$ increased, respectively, by 50% (from 9.4 to 14.1 mg/L) and 46% (from 256 to 374 mg/L · h) when a 600mg tablet was administered with a high fat meal compared with fasting conditions.[32]

• The bioavailability of Chinese rifapentine may vary considerably. In one clinical study, the bioavailability of 2 different batches of Chinese rifapentine were found to be approximately 56 and 73% that of rifapentine of western origin.[33-35]

Distribution

• Rifapentine was 97.7% bound to plasma proteins, primarily albumin, in healthy volunteers.[29,36] In patients (n = 351) receiving rifapentine-based combination therapy for tuberculosis, the volume of distribution of rifapentine was estimated to be 70.2L.[29]

• Except in bone, brain and testicular tissue, rifapentine concentrations in tissue exceeded plasma concentrations in rats at 8, 24 and 72 hours after oral administration of a 10 mg/kg dose.[37] Brain concentrations were <20% of plasma concentrations.

• CSF concentrations of rifapentine were below the limit of detection (<0.15 mg/L) and mean serum concentrations were 7.2 mg/L 10 hours after oral administration (dose not specified) in 5 Chinese patients with tuberculous meningitis.[38]

Metabolism and Elimination

• The mean elimination half-life ($t_{½\beta}$) of rifapentine in 20 healthy male volunteers was 13.2 hours.[26,27] In 14 healthy elderly male volunteers $t_{½\beta}$ was 19.6 hours ($p < 0.05$ *vs* young volunteers).[27]

• 70.2% and 16.6% of a 600mg dose of ^{14}C-rifapentine was recovered from the faeces and urine of 4 healthy volunteers, respectively.[36] In another study 11.2% of a 600mg dose was recovered from urine within 72 hours.[39] There is evidence of enterohepatic recycling in humans.[27,31]

• 25-desacetylrifapentine, the major metabolite of rifapentine, has antimycobacterial activity.[18] Mean C_{max} and AUC_{72} values of 25-desacetylrifapentine were approximately one-third and two-thirds those of the parent compound, respectively.[26]

• Dosage adjustments do not appear to be necessary for rifapentine in patients with hepatic dysfunction.[40] The $t_{½\beta}$ and $AUC_{0-\infty}$ after a single 600mg dose of rifapentine increased by 67 and 19%, respectively, in patients with moderate to severe liver dysfunction (n = 8; $t_{½\beta}$ = 26.5 hours; $AUC_{0-\infty}$ = 381 mg/L · h) compared with healthy subjects in a historical control group (n = 20; $t_{½\beta}$ = 15.9 hours; $AUC_{0-\infty}$ = 319 mg/L · h).[40] Plasma concentrations 24 hours after administration were similar in both groups (5.6 *vs* 5.5 mg/L in healthy controls and patients with hepatic dysfunction, respectively).[40]

Drug Interactions

• Rifapentine induces hepatic microsomal enzymes (cytochrome P450 3A4 and 2C8/9) and has the potential to alter the pharmacokinetics of other drugs.[29] The C_{max} and AUC of indinavir 800mg 3 times daily decreased by 55 and 70%, respectively, when given with rifapentine 600mg twice weekly.[29] Indinavir did not alter the pharmacokinetics of rifapentine. Clearance of antipyrine increased from 2.5 to 4 L/h and its $t_{½\beta}$ decreased from 13.2 to 7.7 hours in healthy volunteers receiving rifapentine 600mg every other day for 10 days.[41] The $t_{½\beta}$ and clearance of antipyrine returned to baseline within 12 days of rifapentine withdrawal. Rifapentine does not induce its own metabolism.[29,41]

• Cytochrome P450 3A-mediated 6β-hydroxylation of testosterone increased by 92 to 335% when primary human hepatocytes were incubated with rifapentine (5 to 50 μmol/L).[42] However, rifapentine had no effect on cytochrome P450 2D6 activity, as measured by dextromethorphan *O*-demethylation, in the same *in vitro* system.[42]

3. Therapeutic Trials

Antitubercular regimens containing rifapentine and rifampicin have been compared in nonblind randomised trials in patients with pulmonary tuberculosis. The tablet formulation (Priftin®) was used in studies conducted in North America and South Africa (hereafter referred to as Western studies) and the capsule formulation was used in studies conducted in China and Hong Kong. In 1 Western study, patients received 6 months of combination therapy, comprising a 2-month intensive phase and a 4-month continuation phase, after which patients were followed-up for 2 years (fig. 2).[29] A second Western study used the same continuation and follow-up schedule as described above; however, therapy during the 2-month intensive phase was left to the discretion of individual investigators.[43,44] In Chinese studies, patients received 9 months of combination therapy, consisting of a 1- or 2-month intensive phase and a 7- or 8-month continuation phase, with 3 years of follow-up (fig. 3).[45,46] In the Hong Kong study, patients received 2 months of intensive therapy with rifampicin, isoniazid, pyrazinamide and streptomycin 3 times/week and then a 4-month rifapentine- or rifampicin-based continuation regimen, after which they were monitored for a median period of 31 months (range 6 to 48 months).[34]

Western Studies (Interim Results)

Sputum Conversion Rates

• At the end of treatment, 87 and 81% of patients treated with rifapentine- or rifampicin-based regimens had negative sputum cultures for *M. tuberculosis* (fig. 2).[29] Only, 4 of 286 (1%) and 8 of 284 (3%) patients treated with the rifapentine- or rifampicin-containing regimens failed to become sputum culture-negative.

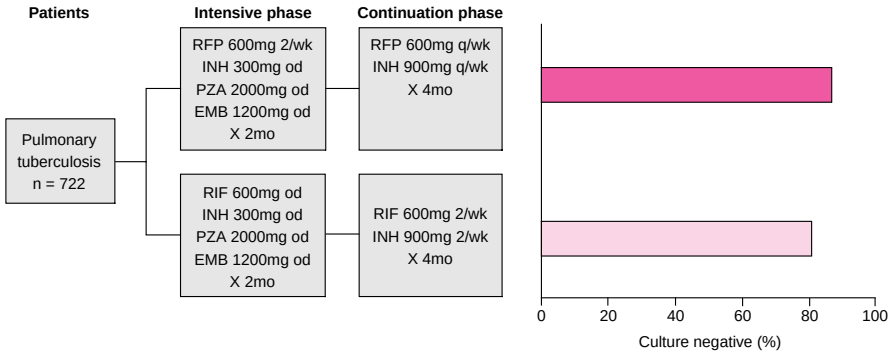


Fig. 2. Intensive and continuation phase regimens and results (at the end of treatment) in a randomised clinical trial with the tablet formulation of rifapentine (Priftin®) in patients with pulmonary tuberculosis.[29] Dosages presented in the figure were those for patients ≥50kg. Patients <50kg received RFP 600mg twice weekly or daily RIF 450mg plus daily INH 300mg, PZA 1500mg and EMB 800mg during the intensive phase (EMB was discontinued once baseline susceptibility tests were available) and RFP 600mg plus INH 600mg once weekly or RIF 450mg plus INH 600mg twice weekly during the continuation phase. Culture conversion data presented are from 286 and 284 evaluable patients, respectively who completed therapy with rifapentine- or rifampicin- based regimens. **EMB** = ethambutol, **INH** = isoniazid; **od** = once daily; **PZA** = pyrazinamide; **RIF** = rifampicin; **RFP** = rifapentine; **q/wk** = once weekly; **2/wk** = twice weekly.

Relapse Rates

• Relapse rates were higher in the rifapentine-treated group (10%) than the rifampicin-treated group (5%) during follow-up.[29] However, poor compliance with other non-rifamycin antituberculosis drugs during the intensive phase of therapy was apparently greater in the rifapentine group (data not available) and this factor appears to be largely responsible for the higher relapse rates. Failure to sterilise sputum during the intensive phase with either regimen predisposed patients to relapse. Importantly, rifampicin resistance was not detected in rifapentine-treated patients who relapsed.

• In another ongoing Western study, 2-fold higher relapse rates in HIV-positive patients with pulmonary tuberculosis who were treated with once-weekly rifapentine plus isoniazid versus twice-weekly rifampicin plus isoniazid during the continuation phase of therapy prompted the study investigators to stop enrolling HIV-positive patients.[43] During 2-years of follow-up, 5 of 36 recipients of the rifapentine-based regimen and 2 of 36 recipients of the rifampicin-based regimen relapsed; rifampicin-resistant strains were documented in 4 recipients of the rifapentine-based regimen versus no patients receiving the rifampicin-based regimen.[43] HIV-positive patients who relapsed had significantly lower CD4+ cell counts at baseline than patients who did not relapse (89 *vs* 225; p = 0.03).[44] Furthermore, a multivariate analysis showed that relapse in HIV-positive patients was associated with the presence of extrapulmonary disease at baseline and use of azole antifungal agents.[44]

China/Hong Kong Studies

Sputum Conversion Rates

• Sputum culture conversion rates were similar in patients treated with regimens containing rifapentine administered once or twice weekly (98 to 100%) or rifampicin once daily or twice weekly (95.7 to 100%; fig. 3) during the continuation phase.[45,46] In 1 study, sputum cultures were not performed on all patients at the end of the study; however, sputum smears were negative in 96 and 97% of patients treated with rifapentine and rifampicin, respectively, at the end of treatment.[46]

• 68 patients with relapsed tuberculosis were included in 1 study.[45] At the end of treatment, 94.4 and 95.3% of those receiving rifapentine once or twice weekly, and 93.8 and 100% of those receiv-

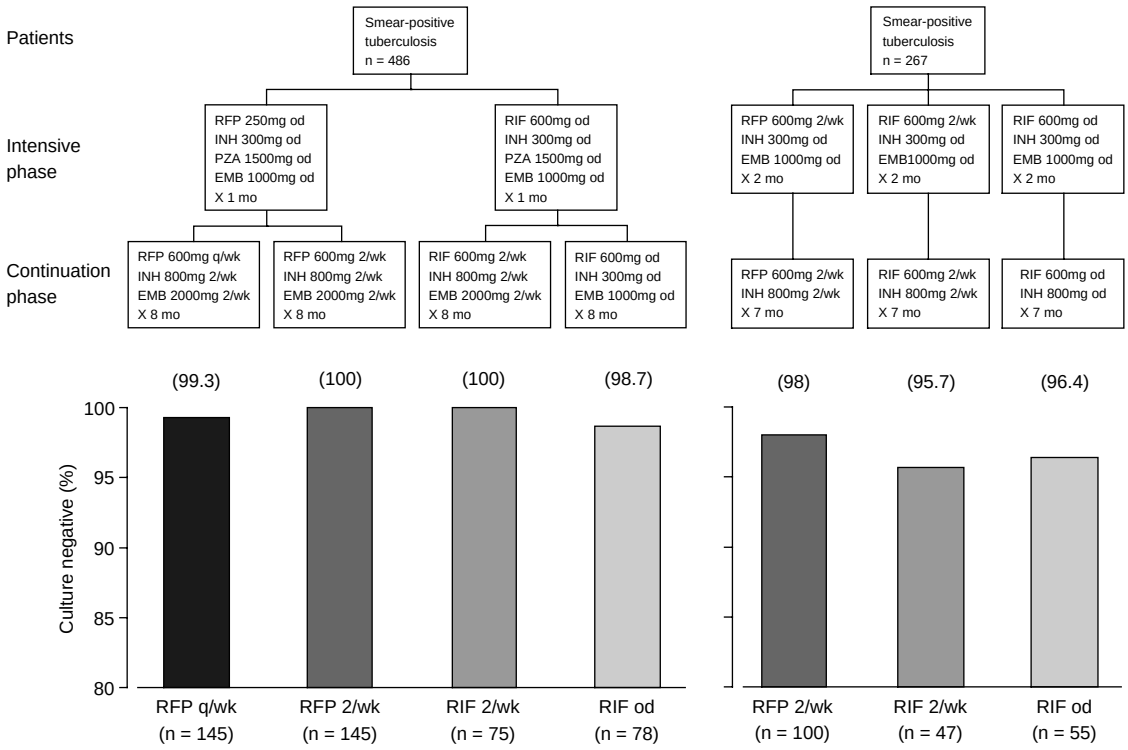


Fig. 3. Intensive and continuation phase regimens and results (at the end of treatment) in 2 randomised Chinese clinical trials.[45,46] Patients were receiving initial treatment for pulmonary tuberculosis. Dosages presented in the figure are those for patients >55kg. Patients ≤55kg in the study by Yan et al.[45] (left) received: EMB 750mg daily or 1500mg twice weekly; INH 700mg twice weekly; RIF 450mg daily; RFP 200mg daily or 500mg once or twice weekly. Patients ≤55kg in the study by He et al.[46] (right) received: EMB 750mg daily or 1500mg twice weekly; INH 300mg daily or 700mg twice weekly; RIF 600mg daily or twice weekly; RFP 600mg twice weekly. Numbers at the bottoms of bars indicate the number of patients from which sputum cultures were obtained at the end of therapy (in one trial follow-up sputum cultures were obtained only from patients who had positive sputum cultures prior to treatment).[46] **EMB** = ethambutol; **INH** = isoniazid; **od** = once daily; **PZA** = pyrazinamide; **RIF** = rifampicin; **RFP** = rifapentine; **q/wk** = once weekly; **2/wk** = twice weekly.

ing rifampicin twice weekly or once daily were sputum culture-negative.

Radiological Results

- Some degree of radiological improvement in pulmonary lesions was documented in all but 3 of 443 evaluable patients (99.3%) in one trial.[45] There was no significant difference between treatment groups in the number of patients whose pulmonary lesions had either completely resolved or had decreased in size by ≥50% at the end of therapy in this study (86 and 84% of rifapentine once- and twice-weekly recipients, and 88 and 85.9% of rifampicin twice-weekly and once-daily recipients, respectively). In the second trial, the respective lesion response rates (no definition given) were 73% in rifapentine recipients and 74.5 and 80.9% in rifampicin twice-weekly and once-daily recipients.[46]

- In patients with cavitary disease (n = 192), the cavity closure rate was 89.4% across all treatment groups with rates of 88.9 and 91.7% in patients receiving rifapentine once or twice weekly.[45] In another study, closure rates were lower in patients

with cavitary disease (n = 122): 76.8% in rifapentine recipients, and 59.3 and 79.5% in rifampicin twice-weekly and once-daily recipients, respectively.[46] In retreated patients with cavitary disease (n = 46) respective cavity closure rates were 73.7 and 80% in rifapentine once- and twice-weekly recipients, and 33.3 and 63.6% in rifampicin twice-weekly and once-daily recipients.[45]

Relapse Rates

- Relapse was documented in 0.75 to 2.6% of patients treated with rifapentine once or twice weekly and 1.4 to 3.8% of patients treated with rifampicin twice weekly or daily during the continuation phase. Relapse was detected by x-ray changes[45,46] and a positive sputum smear and/or culture[45] during 3 years of follow-up.

- In the Hong Kong study, patients with sputum-positive tuberculosis received intensive therapy 3 times/week for 2 months with a rifampicin-based, 4-drug regimen and continuation therapy which comprised 4 months of either rifampicin 600mg and isoniazid 800mg (600mg for patients <43kg) 3 times/week (n = 190), or rifapentine 600mg plus isoniazid given once weekly (n = 199) or 2 weeks out of 3 (n = 203) to simulate poor compliance with the once-weekly regimen.[34] Relapse rates in patients completing both phases of treatment were as follows: 4.1% (7 of 172) in patients treated with rifampicin-based continuation therapy, and 8.9% (16 of 179) and 10.4% (19 of 183), respectively, in patients who received rifapentine-based therapy either weekly or during 2 out of 3 weeks. The bioavailability of the Chinese formulation of rifapentine used in the trial varied considerably, hence, the dosage was increased from 600 to 900mg and subsequently reduced to 750 mg/dose.[33-35] Patients receiving the lower dosage of rifapentine had a higher propensity for relapse.

4. Tolerability

- The most common treatment-related adverse event documented in 1 Western study was hyperuricaemia, which occurred in 21.3% of rifapentine recipients and 15.2% of rifampicin recipients.[29] However, treatment-related hyperuricaemia was only detected during the intensive phase of therapy, during which all patients received pyrazinamide. Increased ALT and AST levels, occurred, respectively, in 5.3 and 4.4% of rifapentine recipients and in 6.6 and 6.4% of rifampicin recipients. Neutropenia was detected in 5% of patients in each group.[29]

- An immune-mediated, influenza-like syndrome has been associated with high doses and/or intermittent administration of rifampicin.[11] Haemolysis and acute renal failure have occurred in severe cases. Four rifampicin recipients experienced an 'influenza-like syndrome' (symptoms not described) in a Chinese study; in 2 patients the reaction was severe and warranted withdrawal from the study.[46] In another study with Chinese rifapentine, mild reactions occurred in 1 rifampicin and 1 rifapentine recipient; treatment was not modified in either patient.[34]

- Rifapentine is teratogenic in rats and rabbits.[29] Major malformations of the cardiovascular, musculoskeletal and reproductive systems were documented in the offspring of animals treated during pregnancy with doses similar to those used in humans (on the basis of body surface area).[29]

5. Rifapentine: Current Status

Rifapentine is approved for the treatment of tuberculosis in the US. The drug is also used in China. Rifapentine has a long half-life which allows for once-weekly administration. When administered twice weekly during the intensive phase and once weekly during the continuation phase, rifapentine has demonstrated efficacy in the treatment of pulmonary tuberculosis in immunocompetent patients.

References

1. Heifets LB, Lindholm-Levy PJ, Flory MA. Bactericidal activity *in vitro* of various rifamycins against *Mycobacterium avium* and *Mycobacterium tuberculosis*. Am Rev Respir Dis 1990 Mar; 141: 626-30
2. Fattorini L, Vincent V, Li B, et al. Type frequency and antimicrobial susceptibility of *Mycobacterium avium-intracellulare* complex strains isolated in Italy from AIDS and non-AIDS patients. J Chemother 1996; 8 (1): 37-42

3. Dickinson JM, Mitchison DA. In vitro activity of new rifamycins against rifampicin-resistant *M. tuberculosis* and MAIS-complex mycobacteria. Tubercle 1987 Sep; 68: 177-82
4. Neu HC. Antibacterial activity of DL 473, a C3-substituted rifamycin derivative. Antimicrob Agents Chemother 1983 Sep; 24: 457-60
5. Arioli V, Berti M, Carniti G, et al. Antibacterial activity of DL 473, a new semisynthetic rifamycin derivative. J Antibiot Tokyo 1981 Aug; 34: 1026-32
6. García-Rodríguez JA, Muñoz Bellido MJ, Fresnadillo MJ, et al. *In vitro* activities of new macrolides and rifapentine against *Brucella* spp. Antimicrob Agents Chemother 1993 Apr; 37: 911-3
7. Schülin T, Wennersten CB, Ferraro RC, et al. Susceptibility of *Legionella* spp. to ketolide HMR 3647 and other newer antimicrobials [abstract no. F-250]. Abstr Intersci Conf Antimicrob Agents Chemother 1997 Sep - Oct 1 28: 188
8. Felmingham D, Robbins MJ, Clark S. The *in vitro* activity of rifampicin and rifapentine against recent clinical bacterial isolates [abstract no. F-35]. Abstr Intersci Conf Antimicrob Agents Chemother 1997 28 Sep-1 Oct: 152
9. Morosini MI, Negri MC, Loza E, et al. Anti-pneumococcal activity of rifapentine [abstract no. E-52]. Abstr Intersci Conf Antimicrob Agents Chemother 1997 28 Sep-1 Oct: 122
10. Araujo FG, Khan AA, Remington JS. Rifapentine is active *in vitro* and *in vivo* against *Toxoplasma gondii*. Antimicrob Agents Chemother 1996 Jun; 40: 1335-7
11. Farr BM. Rifamycins. In: Mandell GL, Bennett JE, Dolin R, editors. Mandell, Douglas and Bennett's Principles and practice of infectious diseases. 4th ed. New York: Churchill Livingstone, 1995: 317-29
12. Venkataraman P, Paramasivan CN, Prabhakar R. *In vitro* activity of rifampicin, rifapentine and rifabutin against south Indian isolates of *Mycobacterium tuberculosis*. Indian J Tuberc 1993; 40 (1): 17-20
13. Yates MD, Collins CH. Comparison of the sensitivity of mycobacteria to the cyclopentyl rifamycin DL473 and rifampicin. J Antimicrob Chemother 1982 Aug; 10: 147-50
14. Moghazeh SL, Pan X, Arain T, et al. Comparative antimycobacterial activities of rifampin, rifapentine, and KRM-1648 against a collection of rifampin-resistant *Mycobacterium tuberculosis* isolates with known *rpoB* mutations. Antimicrob Agents Chemother 1996 Nov; 40: 2655-7
15. Park YK, Cho SH, Shim MS, et al. Detection of rifampicin resistance in *Mycobacterium tuberculosis* by line probe assay [abstract no. U-16]. Abstr 97th Gen Meet Am Soc Microbiol, Miami Beach, Florida 1997 May 4-8: 546
16. Williams DL, Spring L, Miller L, et al. Role of mutations in the *rpoB* of *Mycobacterium tuberculosis* and development of rifamycin cross-resistance [abstract no. U-8]. Abstr 97th Gen Meet Am Soc Microbiol, Miami Beach, Florida 1997 May 4-8: 545
17. Pascual A, Tsukayama D, Kovarik J, et al. Uptake and activity of rifapentine in human peritoneal macrophages and polymorphonuclear leukocytes. Eur J Clin Microbiol 1987 Apr; 6: 152-7
18. Mor N, Simon B, Mezo N. Comparison of activities of rifapentine and rifampin against *Mycobacterium tuberculosis* residing in human macrophages. Antimicrob Agents Chemother 1995 Sep; 39: 2073-7
19. Easmon CS, Crane JP. Comparative uptake of rifampicin and rifapentine (DL473) by human neutrophils. J Antimicrob Chemother 1984 Jun; 13: 585-91
20. Dhillon J, Dickinson JM, Guy JA, et al. Activity of two long-acting rifamycins, rifapentine and FCE 22807, in experimental murine tuberculosis. Tuber Lung Dis 1992 Apr; 73: 116-23
21. Truffot-Pernot C, Grosset J, Bismuth R, et al. Activity of intermittently administered rifampicin and cyclopentyl rifamycin (or DL473) on experimental tuberculosis in the mouse [in French]. Rev Fr Mal Respir 1983; 11: 875-82
22. Grosset J, Lounis N, Truffot-Pernot C, et al. Once-weekly rifapentine-containing regimens for treatment of tuberculosis in mice. Am J Respir Crit Care Med 1998 May; 157 (5): 1436-40
23. Ji B, Truffot-Pernot C, Lacroix C, et al. Effectiveness of rifampin, rifabutin, and rifapentine for preventive therapy of tuberculosis in mice. Am Rev Respir Dis 1993 Dec; 148 (Pt 1): 1541-6
24. Chapuis L, Ji B, Truffot-Pernot C, et al. Preventive therapy of tuberculosis with rifapentine in immunocompetent and nude mice. Am J Respir Crit Care Med 1994 Nov; 150 (Pt 1): 1355-62
25. Kelly BP, Furney SK, Jessen MT, et al. Low-dose aerosol infection model for testing drugs for efficacy against *Mycobacterium tuberculosis*. Antimicrob Agents Chemother 1996 Dec; 40: 2809-12
26. Keung ACF, Eller MG, Gardner S, et al. Pharmacokinetics of rifapentine in young women and elderly men [abstract]. 36th Interscience Conference on Antimicrobial Agents and Chemotherapy 1996 Sep 15: 18
27. Keung ACF, Eller MG, Weir SJ. Single-dose pharmacokinetics of rifapentine in elderly men. Pharm Res 1998; 15 (8): 1286-91
28. Keung AC-F, Miller TD, Green VI, et al. Bioavailability and food effect study of rifapentine in healthy adults [abstract]. Pharm Res 1995 Sep; 12 Suppl.: S-419
29. Data on file. Hoechst Marion Roussel, Inc. Kansas City (MO), USA
30. Chan SL, Yew WW, Porter JHD, et al. Comparison of Chinese and Western rifapentines and improvement of bioavailability by prior taking of various meals. Int J Antimicrob Agents 1994 Jan; 3: 267-74
31. Taglietti M, Frigo GM, Cavenaghi L, et al. Pharmacokinetics of rifapentine in healthy volunteers [abstract no. 1015]. 28th Interscience Conference on Antimicrobial Agents and Chemotherapy 1988 October: 290
32. Owens RCJ, Keung AC-F, Gardner S, et al. Pharmacokinetic and food effect evaluation of rifapentine in subjects seropositive for the human immunodeficiency virus [abstract no. A-2]. Interscience Conference on Antimicrobial Agents and Chemotherapy 1997 37:1
33. Tam CM, Chan SL, Lam CW, et al. Bioavailability of Chinese rifapentine during a clinical trial in Hong Kong. Int J Tuberc Lung Dis 1997 Oct; 1 (5): 411-6
34. Tam CM, Chan SL, Lam CW, et al. Rifapentine and isoniazid in the continuation phase of treating pulmonary tuberculosis initial report. Am J Respir Crit Care Med 1998; 157: 1726-33
35. O'Brien RJ, Vernon AA. New tuberculosis drug development. How can we do better? Am J Respir Crit Care Med 1998; 157: 1705-7
36. Reith K, Keung A, Toren PC, et al. Disposition and metabolism of 14C-rifapentine in healthy volunteers. Drug Metab Dispos 1998; 26 (8): 732-8
37. Assandri A, Ratti B, Cristina T. Pharmacokinetics of rifapentine, a new long lasting rifamycin, in the rat, the mouse and the rabbit. J Antibiot Tokyo 1984 Sep; 37: 1066-75
38. Zhen QP, Chen P, Fen JL, et al. High performance liquid chromatographic determination of anti-tuberculosis drugs in hu-

man body fluids. J Liq Chromatogr Relat Techno 1997; 20 (3): 459-69
39. Zhang Q, Cao Y, Zhang Y. Clinical pharmacokinetic study on rifapentine [in Chinese]. Chin J Antibiotics 1994; 19 (6): 456-8
40. Keung ACF, Eller MG, Weir SJ. Pharmacokinetics of rifapentine in patients with varying degrees of hepatic dysfunction. J Clin Pharmacol 1998; 38: 517-24
41. Vital-Durand D, Hampden C, Boobis AR, et al. Induction of mixed function oxidase activity in man by rifapentine (MDL 473), a long-acting rifamycin derivative. Br J Clin Pharmacol 1986 Jan; 21: 1-7
42. Li AP, Reith MK, Rasmussen A, et al. Primary human hepatocytes as a tool for the evaluation of structure-activity relationship in cytochrome P450 induction potential of xenobiotics: evaluation of rifampin, rifapentine and rifabutin. Chemico-Biological Interactions 1997; 107: 17-30
43. Vernon A, Villarino E, O'Brien R, et al. Relapse with rifampin mono-resistant TB (RMR-TB) in HIV-positive TB patients treated with a once weekly rifapentine -containing regimen [abstract no. 357-PA02]. Int J Tuberc Lung Dis 1997; 1 (5) Suppl. A: S51-2
44. Vernon A, Khan A, Bozeman L, et al. Update on US public health service (USPHS) study 22: a trial of once weekly isoniazid (INH) & rifapentine (RPT) in the continuation phase of TB treatment [abstract]. Am J Respir Crit Care Med 1998 Mar; 157 (3 Pt 2): A467
45. Yan BY et al. A controlled clinical trial of rifapentine containing chemotherapy regimens for bacillary tuberculosis: results at three years [in Chinese]. Chin J Antibiotics 1992; 17 (5): 313-22
46. He GJ et al. A comparative study of rifapentine treatment and three years follow-up on initial pulmonary tuberculous [in Chinese]. Chung Hua Chieh Ho Ho Hu Hsi Tsa Chih 1993 Feb; 16: 73-6,122

Correspondence: *Blair Jarvis*, Adis International Limited, 41 Centorian Drive, Private Bag 65901, Mairangi Bay, Auckland 10, New Zealand.
E-mail: demail@adis.co.nz