Rifapentine for the Treatment of Pulmonary Tuberculosis

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Rifapentine is a recently approved antituberculosis drug that has not yet been widely used in clinical settings. Clinical data support intermittent use of rifapentine with isoniazid during the continuation phase of tuberculosis treatment. Patients with culture-positive, noncavitary, pulmonary tuberculosis whose sputum smear is negative for acid-fast bacilli at the end of the 2-month intensive treatment phase are eligible for rifapentine therapy. Rifapentine should not be used in human immunodeficiency virus–infected patients, given their increased risk of developing rifampin resistance with currently recommended dosages. Rifapentine is not currently recommended for children aged <12 years, pregnant or lactating women, or individuals with culture-negative or extrapulmonary tuberculosis. Rifapentine (600 mg) is administered once weekly with isoniazid (900 mg) during the continuation phase of treatment. This combination should only be given under direct observation. As with rifampin, drug-drug interactions are common, and regular patient monitoring is required. Ease of administration makes this regimen attractive both for tuberculosis-control programs and for patients.

Use of directly observed therapy (DOT) for the treatment of tuberculosis improves treatment completion and is recognized as the standard of care in the United States [1–3]. In its strictest sense, DOT entails the observation of patients while they ingest every dose of medication prescribed. This may overburden the human resources available to the provider or the local tuberculosis-control program. Arguably, if the frequency of drug administration were reduced to once per week, while the efficacy of treatment was maintained, the implementation of DOT would be easier [4, 5]. Introduction of rifapentine (Priftin; Sanofi-Aventis), a rifamycin with a relatively long half-life, which allows for once-weekly dosing, may hold the answer to this conundrum.

Despite its approval by the US Food and Drug Administration (FDA) in 1998 for the treatment of pulmonary tuberculosis, rifapentine is rarely used by clinicians in New York City. Current US national tuberculosis treatment guidelines recommend rifapentine for the treatment of tuberculosis in carefully selected patients [6]. The once-weekly regimen is likely to facilitate DOT, given the simplicity of administration and the convenience of the regimen to patients.

Because administration of rifapentine is new for many physicians, a review is in order. We provide an overview of pharmacological aspects of rifapentine, suggest an algorithm for its use, and discuss future prospects for rifapentine.

CLINICAL PHARMACOLOGY

Rifapentine is a cyclopentyl-substituted semisynthetic rifamycin that was first synthesized in 1965 by the Italian company that developed rifampin. Figure 1 presents the chemical structures of rifampin and rifapentine.

Mechanism of action. Like other rifamycins, rifapentine inhibits bacterial DNA-dependent RNA polymerase [7]. Rifamycins are unique among drugs that work by this mechanism, because the inhibition of RNA polymerase will occur even when enzyme exposure to the drug is very brief in otherwise metabolically dormant organisms [8]; this has implications for the use of these drugs for treatment of latent tuberculosis infection (LTBI), as discussed later.

The MIC of rifapentine is ~0.02 µg/mL [9]. The incidence of rifapentine-resistant organisms associated with spontaneous mutations in an otherwise susceptible population of Mycobacterium tuberculosis strains is ~1 in 107–108 bacilli [10]. Resistance develops quickly when exposed to a single drug [8]. The development of resistance to rifampin—and, by extension, to rifapentine, given its complete cross-resistance to rifampin [10]—is usually attributable to a single base-pair mutation in the β subunit of the RNA polymerase gene (rpoB) [11, 12].
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Therefore, rifamycins should only be used in combination with other drugs when treating active tuberculosis disease.

**Pharmacokinetics.** After oral administration, rifapentine is well absorbed from the gastrointestinal tract, reaching peak serum concentrations in 5–6 h. The mean rifapentine elimination half-life ranges from 13.2 to 14.1 h. The active metabolite reaches peak concentration in 14.4–17.8 h, and the mean elimination half-life is 13.3–24.3 h. In comparison, rifampin has an elimination half-life of 2–3 h. The maximum plasma concentrations are well above the MICs for *M. tuberculosis* and *Mycobacterium avium* after administration of the standard 600-mg dose [13]. Ingestion of the dose with a high-fat meal increases peak concentrations and the area under the curve by 43%–50% over fasting values [14–16]. The drug is metabolized mostly by the liver and is excreted predominantly (70%) in feces. The drug is metabolized by hydrolysis and deacetylation to 25-O-desacetylrifapentine, which is microbiologically active, contributing 38% of the drug’s overall activity [15].

In a single-dose pharmacokinetic study involving patients with various degrees of hepatic dysfunction, rifapentine was well tolerated, irrespective of the etiology or severity of hepatic dysfunction [17]. Patients with hepatic and/or renal impairment should be monitored closely when taking rifapentine. Because the drug and its metabolite are highly protein bound (98%), hemodialysis would not be expected to enhance their elimination [15, 16].

**CLINICAL TRIALS**

Phase I and II trials conducted in China demonstrated that rifapentine was safe in humans [18]; since then, phase III trials have been conducted (table 1). The Hong Kong Tuberculosis Service conducted a trial that compared 3 regimens: thrice-weekly rifampin plus isoniazid (HR), once-weekly rifapentine plus isoniazid (HP), and once-weekly rifapentine plus isoniazid given every 2 of 3 weeks (HP1.2/3; no medications were given 1 week out of every 3 weeks to simulate nonadherence). These regimens were administered in the continuation phase (months 3–6) of a 6-month regimen in patients with culture-positive, drug-susceptible pulmonary tuberculosis after they had received a 4-drug regimen (isoniazid, rifampin, pyrazinamide, and streptomycin given thrice weekly) during the intensive phase of treatment (i.e., first 2 months of treatment). In an intent-to-treat analysis involving 592 patients, relapse and failure were more common in the HP1 (8.5%; *P* = .04) and in the HP1.2/3 (10.3%; *P* = .01) groups, compared with the HR group (3.7%) group. The drug used in this trial was of Chinese origin and was known to have low bioavailability. The subgroup—for which a higher dose of rifapentine was used, to increase overall drug level—had treatment failure or relapse rates similar to those of the overall study groups. During the 5-year follow-up phase for 534 patients, final adverse effects rates were similar [19–21].

During 1995–1998, an open-label, randomized, multiple-center study of 722 HIV-uninfected patients with pulmonary tuberculosis in South Africa and North America (Protocol 008) was conducted by the manufacturer of rifapentine. This trial compared a rifapentine-based regimen with a rifampin-based regimen, using an improved formulation of rifapentine manufactured in the United States. During the 2-month intensive phase, one group received rifapentine twice weekly (plus isoniazid, pyrazinamide, and ethambutol given daily), and the other received rifampin daily (plus isoniazid, pyrazinamide, and ethambutol given daily). In the continuation phase, the rifapentine-isoniazid group received rifapentine once per week, whereas the rifampin-isoniazid group received rifampin twice per week. Six months after completion of treatment, 25 (10%) of 249 patients in the rifapentine arm experienced relapse, compared with 11 (5%) of 229 patients in the rifampin arm. Most of the rifapentine relapses occurred in patients with poor adherance with the companion medicines during the intensive phase. Relapse in the rifapentine arm was not associated with...
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<td>Intensive phase regimen</td>
<td>Two months of isoniazid, rifampin, pyrazinamide, and streptomycin given thrice weekly</td>
<td>Two months either of daily isoniazid, rifampin, pyrazinamide, and ethambutol or of daily isoniazid, pyrazinamide, and ethambutol plus twice-weekly rifapentine</td>
<td>Two months of daily, twice-weekly, or thrice-weekly isoniazid, rifampin, pyrazinamide, and ethambutol (or isoniazid, rifampin, pyrazinamide, and streptomycin)</td>
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<td>Continuation phase regimen</td>
<td>Either thrice-weekly isoniazid plus rifampin (HR₃) or once-weekly isoniazid plus rifapentine (HP₁); a third group omitted every third dose, to simulate poor compliance (HP₁₂₃)</td>
<td>Either twice-weekly isoniazid-rifampin or once-weekly isoniazid-rifapentine</td>
<td>Either twice-weekly isoniazid-rifampin or once-weekly isoniazid-rifapentine</td>
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<td>Outcomes</td>
<td>Relapse/failure rates, 3.7% (7 of 190 patients) for the HR₃ group, 8.5% (17 of 199) for the HP₁ group, and 10.3% (21 of 203) for the HP₁₂₃ group</td>
<td>Relapse rates, 5% (11 of 229 patients) for the isoniazid-rifampin group and 10% (25 of 249) for the isoniazid-rifapentine group</td>
<td>Relapse/failure rates for HIV-negative patients with no cavitation on chest radiograph, 2.9% (6 of 210 patients) for the isoniazid-rifapentine group and 2.5% (6 of 241) for the isoniazid-rifampin group; for those with cavitation on a chest radiograph, 14.4% (40 of 278) for the isoniazid-rifapentine group and 8.9% (22 of 246) for the isoniazid-rifampin group</td>
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<td>Comments</td>
<td>Patients were randomized after completion of the intensive phase; a formulation of rifapentine with poor bioavailability was used</td>
<td>Patients were randomized before the intensive phase; all patients were HIV uninfected; a high rate of poor adherence was noted during intensive phase</td>
<td>Patients were randomized after completion of the intensive phase; all patients were HIV uninfected; patients were found to be HIV uninfected in the final analysis; a separate arm involving 71 HIV-infected patients was stopped early because of the development of rifamycin monoresistance in only the rifapentine arm</td>
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development of rifamycin resistance in this HIV-uninfected group of patients [16].

The US Public Health Service began a study of rifapentine (Study 22) in 1995 under the aegis of the Centers for Disease Control and Prevention’s Tuberculosis Trials Consortium (TBTC). This study compared once-weekly rifapentine plus isoniazid with twice-weekly rifampin plus isoniazid in the continuation phase of therapy in culture-negative patients who completed standard 2-month intensive therapy (rifampin, isoniazid, and pyrazinamide plus ethambutol or streptomycin). Recruitment in the HIV-infected arm of the study was stopped in March 1997, because 4 of 36 patients enrolled in the once-weekly rifapentine-isoniazid arm had experienced relapse with acquired rifampin-monoresistant tuberculosis [22]. The final analysis of the 803 HIV-uninfected patients who completed the trial revealed that the standard twice-weekly rifampin-isoniazid regimen had similar failure/relapse rates as the once-weekly rifapentine-isoniazid regimen in patients for whom cavitation had not been noted on initial chest radiographs (relapse/failure rate of 2.5% in the twice-weekly rifampin-isoniazid group, compared with 2.9% in the once-weekly rifapentine-isoniazid group; relative risk, 1.15; \( P = .81 \) ) [23]. This finding formed the basis for the current recommendation for using rifapentine and isoniazid in selected patients during the continuation phase of treatment of drug-susceptible pulmonary tuberculosis [6]. Reasons for decreased effectiveness of once-weekly rifapentine-isoniazid (compared with twice-weekly rifampin-isoniazid) in patients with cavitary disease may be that (1) both rifapentine and 25-O-desacytlyrifapentine are highly protein bound, and exposure to available drug may be inadequate with the 600-mg dose; and (2) the isoniazid concentration may have been inadequate [18, 24].

**PATIENTS ELIGIBLE FOR A RIFAPENTINE REGIMEN**

To be eligible for rifapentine therapy, patients must be aged ≥12 years; have culture-positive, noncavitary pulmonary tuberculosis; be infected with isolates susceptible to rifampin, isoniazid, and pyrazinamide; and have sputum smear results negative for acid-fast bacilli at the end of the 2-month intensive phase (figure 2).

All patients with active tuberculosis should be tested for HIV infection. Only HIV-uninfected patients should receive rifapentine; to ensure this, a negative HIV test result must be documented before treatment initiation. Treatment of HIV-infected patients with this highly intermittent regimen for tuberculosis has been associated with the development of rifamycin resistance [22, 25]. Acquired rifamycin resistance did not occur in HIV-uninfected patients [16, 23]. The authors speculate that the long half-life of rifapentine and the very short half-life of isoniazid likely led to exposure to a single drug and to the development of resistance [22]. In addition, a substudy of Study 22 revealed that low plasma concentrations of isoniazid were associated with failure/relapse in the HIV-uninfected patients in the once-weekly rifapentine-isoniazid group; this may also have been applicable to the HIV-infected patients in Study 22. On the basis of these findings, a drug with a duration of activity longer than that of isoniazid may be needed to achieve effective once-weekly therapy with rifapentine in HIV-infected patients [26].

Patients with extrapulmonary tuberculosis only are not candidates for this regimen, because the studies that led to rifapentine’s approval did not include such patients; however, extrapulmonary tuberculosis is frequently paucibacillary and should be amenable to treatment with rifapentine. Mediastinal or hilar lymphadenopathy accompanying an infiltrate is not considered extrapulmonary tuberculosis. Patients with cavity lesions noted on their initial chest radiograph are at increased risk of experiencing relapse if they are treated with once-weekly rifapentine-isoniazid; therefore, such patients should not receive this regimen [23]. Patients with tuberculosis due to organisms resistant only to streptomycine and/or ethambutol can be considered for treatment with rifapentine. Persons with culture-negative pulmonary tuberculosis are not candidates for once-weekly rifapentine-isoniazid therapy, because this regimen has not been evaluated for such patients. There is no reason why culture-negative pulmonary tuberculosis should not respond to rifapentine; however, clinical trials are needed to verify this hypothesis. This regimen has also not been studied in children aged <12 years old or in pregnant or lactating women.

Risk factors for relapse/failure among HIV-uninfected patients with tuberculosis include cavitation noted on the initial chest radiograph and positive results of sputum smear or culture after 2 months of intensive-phase therapy consisting of at least a rifamycin (rifampin or rifabutin), isoniazid, and pyrazinamide [22, 27, 28]. It is reasonable to conclude that patients without these risk factors will fare just as well, regardless of whether they are treated with a rifampin-based regimen or with a regimen based on once-weekly rifapentine in the continuation phase [23].

Candidates for the rifapentine-isoniazid regimen should be educated about the availability of this option early in therapy. Offering a once-weekly regimen to patients provides an opportunity to reintroduce DOT if the patient was not receiving DOT since the commencement of treatment. One to 2 weeks before the end of the 2-month intensive phase of therapy, sputum specimens must be obtained to demonstrate that sputum smear results are negative before the initiation of the regimen. Patients with ≥1 sputum smear that tests positive for acid-fast bacilli at the end of the intensive phase are not candidates for the once-weekly regimen, because these patients are likely to
Figure 2. Treatment of tuberculosis with rifapentine. *A sputum smear should be performed 1–2 weeks before the end of the 2-month intensive phase. Rifampin or rifabutin should not be given twice weekly to HIV-infected patients with CD4 cell counts <100 cells/μL; it should be given either daily during the intensive phase of treatment and either daily or thrice weekly during the continuation phase. *Patients with diabetes, cancer, chronic renal disease, chronic liver disease, alcoholism, preexisting peripheral neuropathy, malnutrition (defined as a body weight ≥10% less than the ideal), or any wasting syndrome may require supplementation with pyridoxine (vitamin B6). *Interruption therapy should only be given with direct observation of treatment. *A missed dose can be given on another day during the week, as long as the subsequent dose is separated from the last dose by at least 72 h. If doses are missed for ≥2 consecutive weeks, the patient should return to a rifampin-based regimen.

respond poorly to treatment [23, 29]. DOT should be arranged through the local health department.

**Dosing.** Rifapentine should be given with isoniazid during the continuation phase of the treatment of drug-susceptible pulmonary tuberculosis after an intensive phase that consists of at least rifampin (or rifabutin), isoniazid, pyrazinamide, and ethambutol administered for 2 months. Ethambutol can be discontinued when susceptibility to the other 3 drugs is confirmed. Although rifapentine is approved for treatment in both phases of pulmonary tuberculosis, US national guidelines do not recommend its use during the intensive phase at present [6].

Rifapentine is available as 150-mg film-coated tablets. The currently recommended dosage is 600 mg weekly, always administered with isoniazid (900 mg weekly); there is indication in both human and mouse models that higher doses of rifapentine (900–1200 mg) may have better bactericidal activity [30–32]; however, the optimal dose remains to be determined. Higher doses have been well tolerated in small groups of patients [32, 33].

Administration of rifapentine with food improves its absorption and may be useful for patients who are experiencing nausea, vomiting, or other gastrointestinal upset [16]; however, administration with food decreases isoniazid concentrations by 20%–50% (peak concentration) [34–36]. The interaction of food and coadministered isoniazid and rifapentine requires additional study. Low isoniazid concentrations have been associated with failure/relapse, thus presenting a dilemma [26]. This problem could be solved by administration of moxifloxacin instead of isoniazid, because moxifloxacin has a long half-life, and its absorption is not affected by food [37]; however, this regimen requires investigation.

**Treatment length.** Treatment for pulmonary tuberculosis caused by drug-susceptible organisms lasts at least 6 months. If an appropriate candidate starts to receive a regimen of rifapentine plus isoniazid and later has positive results of cultures of sputum samples obtained at the end of or after the intensive phase of therapy, it is recommended that the total length of therapy be increased to 9 months, with at least 28 doses of rifapentine and isoniazid administered in the continuation phase [6].

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ADVERSE EFFECTS

Rifamycins can occasionally cause drug-induced hepatitis and have rarely been associated with severe thrombocytopenia. In clinical trials, rates of adverse reactions were similar for rifampin and rifapentine, with increased aminotransferase activity seen in ~5% of all patients [16]. Rifapentine, like other rifamycins, may produce an orange-red discoloration of body fluids (urine, tears, sputum, saliva, feces, and CSF). Contact lenses and dentures can become permanently stained.

Patients should undergo baseline testing of serum transaminase and bilirubin concentrations, as well as a complete blood cell count at the beginning of tuberculosis therapy. Monthly follow-up blood testing is not necessary for most patients if the baseline values are normal, unless a patient develops symptoms consistent with an adverse drug reaction. Therapeutic levels of rifampin have been known to interfere with assays for vitamin B₁₂ and folate; similar interactions should be considered for rifapentine [16].

Drug interactions. Rifapentine, like other rifamycins, induces the cytochrome P450 system of enzymes—specifically, the CYP3A4, CYP2C8, and CYP2C9 isozymes [15]. The relative potencies are as follows: rifampin, 1; rifapentine, 0.85; and rifabutin, 0.40. Therefore, rifapentine enhances the metabolism and can markedly lower serum concentrations of drugs that are metabolized by these enzymes [16]. One study suggests that the maximal induction of these enzymes occurs within 4 days after receipt of the first dose and returns to the baseline level within 14 days after rifapentine is discontinued [38]; however, despite limited data, there is no reason to expect rifapentine to induce enzymes faster than rifampin (which requires at least 7 days) [39, 40]. Any drug known to have interactions with rifampin (e.g., oral contraceptives, methadone, β-blockers, benzodiazepines, and oral anticoagulants) should be considered to have similar interactions with rifapentine, unless proven otherwise.

Use in pregnant women, lactating mothers, and children. Rifapentine is teratogenic in rats and rabbits given anything from 0.3 to 1.3 times the human dose of rifapentine [16]. There are no adequate data on its use in pregnant women, and its effect on the human fetus is unknown. In the Protocol 008 study, 6 patients randomized to rifapentine became pregnant while taking rifapentine; 2 had normal deliveries, 2 had spontaneous abortions in the first trimester, 1 had an elective abortion, and 1 was lost to follow-up [16]. As a precaution, rifapentine should not be used in pregnant women. If a woman becomes pregnant while receiving rifapapentine, we recommend that the regimen be changed to rifampin-isoniazid. It is not known whether rifapentine is excreted in human milk; therefore, rifapentine is not recommended for lactating mothers.

Data on the safety and efficacy of rifapentine in children aged <12 years are limited; therefore, this drug should not be administered to them. One study has shown that children may need larger weight-normalized doses [41]. Children aged ≥12 years should receive the same dose as adults [6]. Additional pharmacokinetic studies are underway, including US Public Health Service Study 26, which has been extended to include children.

Follow-up after treatment completion. In general, follow-up is not required after completion of treatment, because relapse is uncommon after the use of rifampin-based or rifapentine-based regimens in the subgroup of patients for whom it is currently recommended [6]. To document cure, culture samples should be obtained at the end of treatment [6]. If symptoms of tuberculosis develop after treatment has been completed, a full evaluation, including culture and susceptibility testing, should be performed.

FUTURE PROSPECTS FOR RIFAPENTINE

Beyond the currently recommended limited uses, there is greater potential for rifapentine that warrants further investigation. The drug has been studied in murine models of both active tuberculosis and LTBI and shows promise in being able to decrease treatment duration, reduce the number of doses administered, and potentially decrease relapse rates [31, 42].

Observational studies have demonstrated that relapse rates for active tuberculosis may be higher with rifampin-based intermittent regimens than for daily regimens [28, 43]. A once- or twice-weekly regimen with better efficacy would be of great value, because it could substantially reduce the cost of DOT. One study of active tuberculosis in mice showed that twice-weekly therapy with rifapentine, moxifloxacin, and pyrazinamide was significantly more active in both the intensive and continuation phase of treatment than was a rifampin- and isoniazid-based regimen given twice weekly [31]. Another murine study showed that once-weekly moxifloxacin-rifapentine treatment administered during the continuation phase was more active than a twice-weekly isoniazid-rifampin regimen [30]. The best effect was noted for dosages of rifapentine equivalent to a human dosage of 900 mg or 1200 mg twice weekly. This and other murine studies show that coadministration of isoniazid with the combination of moxifloxacin, a rifamycin, and pyrazinamide reduces the efficacy of the combination, suggesting that isoniazid has an antagonistic effect on the combination [31, 44]. A combination of rifapentine and moxifloxacin is well suited for intermittent therapy, because both drugs have long half-lives.

In an LTBI model, a 3-month once-weekly regimen of rifapentine plus either isoniazid or moxifloxacin was as effective as a daily regimen of isoniazid for 6–9 months [42]. A short LTBI treatment regimen that requires only 12 doses would be advantageous, because completion rates for 9-month regimens are notoriously low (Centers for Disease Control and Prevention and New York City Department of Health and Mental
Hygiene, unpublished data) [45, 46]. A regimen of rifapentine (900 mg) plus isoniazid (900 mg) once weekly for 12 weeks is currently being evaluated for the treatment of LTBI in the TBTC study, and rifapentine (900 mg) plus isoniazid (900 mg) once weekly for 12 weeks and rifampin (450–600 mg) plus pyrazinamide (750–1500 mg) daily were also studied in household contacts of patients with tuberculosis in a recent phase II trial [47, 48]. However, because isoniazid use is associated with hepatotoxicity, additional investigation of rifapentine-moxifloxacin is warranted.

CONCLUSIONS

A once-weekly regimen for tuberculosis treatment represents major progress. As the world awaits further progress in tuberculosis therapy, clinicians should utilize all currently available options with DOT. Because experience with rifapentine is limited, tuberculosis-control programs should monitor its use and the outcome of patients over the next few years. Additional studies of rifapentine are necessary for patients with pulmonary and extrapulmonary tuberculosis and LTBI, to identify the optimal dose and frequency of administration.

Acknowledgments

We thank Dr. John Jereb and Dr. Eric Nueremberger for careful review of this manuscript.

Financial support. Bureau of Tuberculosis Control program funds.

Potential conflicts of interest. All authors: no conflicts.

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