Rifapentine

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OVERVIEW

Tuberculosis (TB) continues to be a global burden, and with its link to HIV and associated morbidity, the search continues for effective and convenient therapy. Traditional directly-observed therapy (DOT) and self-supervised therapy are cumbersome and often associated with poor completion and compliance rates. Recent studies on intermittent treatment regimens have better identified patient populations who are appropriate candidates for once or twice-weekly therapy.[1,2]

Rifapentine (RPT), marketed under the brand name Priftin, is a rifamycin-class antibiotic. Rifamycin antimycobacterials include rifampin, rifabutin, and rifapentine, which are often used in combination with other antimicrobials to treat TB.[3] According to the Sanford Guide the RPT dosage is 600 mg by mouth twice weekly for two months in combination with isoniazid (INH), pyrazinamide, and ethambutol in immunocompetent patients and then 600 mg once weekly for four months in combination with INH for drug susceptible TB. The American Thoracic Society/Centers for Disease Control/Infectious Diseases Society of America (ATS/CDC/IDSA) recommend that it be used in the continuation phase or for latent TB.

RPT should not be used as monotherapy for treatment of TB disease since mutational resistance can emerge quickly. It is not recommended in children under 12, in pregnant or lactating women, in individuals with culture negative or extra pulmonary tuberculosis, or in patients with cavitary TB.[3,4]

Currently the CDC recommends INH-RPT regimens for 12 weeks as DOT doses as an equally effective alternative to nine months of daily self-supervised INH treatment for treating latent TB infections in patients older than 12 who have a high likelihood of developing TB. This includes patients who are HIV positive, otherwise healthy, and not on retroviral therapy.[4] INH-RPT intermittent regimens are not recommended for HIV-infected patients who are on antiretroviral therapy, as drug interactions have not been studied.[2,4]

Chang, e*t al.* summarized three studies (two retrospective cohort analyses and one systematic review and meta-analysis) on the impact and efficacy of intermittent dosing in HIV-related TB. They concluded that intermittent treatment, in the *initial phase* of the disease, was associated with a higher risk of treatment failure, relapse, and acquired rifamycin resistance. Therefore, intermittent dosing is not recommended in the initial phase of HIV-related TB (IA recommendation).[5]

Martinson and colleagues conducted an open-label, randomized trial comparing RPT (900 mg) plus INH (900 mg) once weekly for 12 weeks, rifampin (600 mg) plus INH (900 mg) twice weekly for 12 weeks, continuous INH (300 mg) daily for the duration of the study (<6 years), and a control regimen of INH (300 mg) daily for six months. The primary end point was tuberculosis-free survival. The study concluded that rifamycin-based *preventive* treatment has similar, but not superior, efficacy to the six months of INH.[6] For both HIV positive and HIV negative patient

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population, completion rates are higher in INH-RPT intermittent treatment groups and permanent drug discontinuation rates were also lower among those in the INH-RPT treatment group. Discontinuation due to hepatotoxicity was lower in the INH-RPT group compared to INH (0.3% vs. 2.0%).[6]

Adverse reactions, contraindications, drug interactions

Significant adverse reactions include hyperuricemia, hypertension, headache, nausea, diarrhea, rash, hematuria, neutropenia, elevated liver enzymes, arthralgia, and hemoptysis. Prolonged use may result in fungal or bacterial super infection, including *C. difficile* associated diarrhea. RPT may also worsen porphyria and can redden secretions, including urine and tears.*2,4*

RPT is contraindicated in HIV positive patients for treatment of TB disease due to the unacceptable high rate of failure due to acquired mutational resistance and lack of studies with concurrent anti-retroviral therapy. Patients should be counseled that compliance is absolutely necessary. Rifapentine is contraindicated if there is evidence or a history of hypersensitivity to RPT, rifampin, rifabutin, or any rifamycin analog. Caution should be used in patients with hepatic impairment, and liver enzymes and bilirubin should be measured prior to therapy in patients with possible liver disease. Furthermore, liver enzymes and bilirubin should be monitored every two- four weeks during therapy, and if there is any evidence of hepatitis or unacceptable elevation in the liver enzymes or bilirubin, it should be discontinued immediately.[3,4]

Similar to other rifamycins, RPT induces metabolism of many medications, specifically medications primarily metabolized by cytochrome P450 isoenzymes 3A4, 2C8 and 2C9.[2] Careful monitoring of drugs with narrow therapeutic windows (e.g., warfarin, phenytoin) is important while patients are on rifapentine therapy. Women who take hormonal birth control should be counseled to use a barrier back up method while on RPT. It is contraindicated with concurrent antiretroviral therapy, as these interactions have not been studied. RPT is a pregnancy category C drug, and teratogenic effects have been observed in animal reproduction studies. The CDC does not currently recommend rifapentine as part of the treatment regimen due to insufficient data in pregnant woman.[4]

Mechanism of action

RPT inhibits the initiation of chain formation for RNA synthesis by inhibiting DNA-dependent RNA polymerase in susceptible strains of *Mycobacterium tuberculosis* (MTB). It is bactericidal against both intracellular and extracellular bacilli. MTB resistant to other rifamycins, including rifampin, is almost always resistant to rifapentine. Cross-resistance does not appear between rifapentine and other non-rifamycin anti-mycobacterial agents.[2]

Pharmacokinetics

RPT is well absorbed and attains a mean area under the curve of 325 mcg/hr/ml after a 600 mg dose. It is highly protein bound (93-97%) and is metabolized by the liver. It is excreted approximately 70% through the bile and 17% through the urine and has a half-life of 16-19 hours. The time to peak concentration in serum is five-six hours.[2] *In vitro* studies show that there is a significant post-antibiotic effect (PAE) observed with the rifamycins, supporting their use in intermittent treatment regimens. Due to this PAE, intermittent exposure (a few hours) to RPT can suppress mycobacterial growth for several days.[4] The free peak concentration (C_{peak}) to the minimum inhibitory concentration (MIC) ratio correlates best with the PAE and the suppression of resistance. This concentration-dependent activity suggests that high doses given at longer intervals are likely more effective than smaller doses given as daily therapy. RPT is metabolized to an active metabolite 25-desacetyl rifapentine which extends its activity profile.[4,6]

Recent large randomized controlled clinical trials

In 1995-1998 a randomized multicenter trial of non-HIV infected patients with pulmonary tuberculosis was done in South Africa and North America; one group received RPT twice weekly (with INH, pyrazinamide and ethambutol daily) and the other received rifampin daily (with INH, pyrazinamide and ethambutol daily). Although the relapse rate was slightly higher in the RPT arm, the development of resistance was lower.[2] RPT is given with INH during the continuation phase for treatment of drug susceptible pulmonary tuberculosis after being treated with rifampin (or rifabutin), INH, pyrazinamide and ethambutol for two months. US national guidelines do not recommend RPT use in the intensive phase.

In latent tuberculosis infections RPT plus INH or moxifloxacin given for three months once weekly was as effective as INH for six to nine months given daily.[3]

Keypoints

1. RPT is used in the continuation phase in non-cavitary drug susceptible pulmonary tuberculosis.
2. RPT is a long acting drug that can be administered once weekly with INH for latent TB infection and during the continuation phase of active TB.
3. Rifapentine is not recommended in HIV positive patients with active TB infection due to its high relapse rate, development of resistance, and the lack of studies examining concurrent anti-retroviral therapy.

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