Current Report — HIV

Rifabutin Prophylaxis Against *Mycobacterium avium* Complex Disease

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Mycobacterium avium complex (MAC) disease is a common late-stage opportunistic infection of the acquired immunodeficiency syndrome (AIDS).[1] Recently attention has focused on prophylaxis against MAC disease with publication of the results from two multicenter rifabutin prophylaxis trials[2] and the release of a Public Health Service task force recommendation.[3,4] Because MAC disease can contribute to AIDS morbidity and mortality, this *Current Report — HIV* addresses some of the potential benefits and risks of MAC prophylaxis and discusses treatment of MAC disease.

MAC Disease

MAC infection usually is not detected until late in the course of AIDS. One study reported MAC bacteremia in 39 percent of patients with CD4+ lymphocyte counts less than 10 cells/μL, 30 percent for 10–19 cells/μL, 20 percent for 20–29 cells/μL, 15 percent for 40–59 cells/μL, 8 percent for 60–99 cells/μL, and 3 percent for 100–200 cells/μL.[5] At San Francisco General Hospital 96 percent of patients with diagnosed MAC disease have fewer than 50 CD4+ cells/μL (D. Chin, personal communication, 9 November 1993). Indeed, in the current studies that prompted the new recommendations, the median CD4+ count at the time of MAC bacteremia was 12 cells/μL.[2]

Liver, bone marrow, lymph node, bowel, and lung involvement, as well as MAC bacteremia, are characteristic of MAC disease. Symptoms can be generalized or specific to the principal organ system involved. Generalized symptoms include fever, sweats, weight loss, and fatigue. These symptoms are common in late-stage disease and can be caused by other AIDS-related opportunistic infections, malignancies, and the human immunodeficiency virus (HIV) itself. Specific manifestations reflect the organ system affected. Hepatic involvement is characterized by alkaline phosphatase elevation and, at times, hepatic pain, hepatosplenomegaly, and transaminase elevations. Bone marrow infection most often results in anemia. Intra-abdominal, intrathoracic, or peripheral lymph node enlargement can be responsible for pain or mass effect, or it can be asymptomatic. Bowel involvement can produce diarrhea and abdominal pain. Pulmonary MAC infection can contribute to respiratory failure, or it can be an incidental finding of sputum examination after sputum induction or bronchoscopic evaluation. Specific organ system disease can cause generalized symptoms in addition to the specific symptoms and signs.

Patients with clinical symptoms or signs suggestive of MAC disease should receive a standard evaluation for MAC disease and other opportunistic infections and HIV complications. Active MAC disease should be documented by the presence of MAC organisms in tissues or blood whenever possible. The finding of MAC organisms in pulmonary or stool specimens does not necessarily indicate active MAC disease, so clinical correlation is required. Patients with active MAC disease should receive daily multidrug oral therapy with at least two drugs.[3,4] Clarithromycin (1–2 g/d in two divided doses) or azithromycin (500 mg/d) should be included whenever possible. Ethambutol (15 mg/kg/d) is usually chosen as the second drug. If needed, a third or fourth drug can be added for serious illness. These drugs include ciprofloxacin (500–750 mg/d), clofazimine (100 mg/d), and rifabutin or rifampin (450–600 mg/d). Resistant

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isolates have not occurred during rifabutin prophylaxis, so rifabutin can be included as part of the acute treatment regimen. Intramuscular amikacin (7.5 mg/kg/d) has also been used. These recommendations update our previous recommendations[6] for treating acute MAC disease.

Preventing Bacteremia and Selected Symptoms of MAC Disease

The rifabutin prophylaxis studies[2] included a total of 1146 patients with either a CD4+ lymphocyte count of 200 or fewer cells/μL or a previous AIDS-defining event other than MAC disease. Subjects received either placebo or oral rifabutin 300 mg once daily. Treated subjects received the drug for a mean of about 7 months. Monthly blood cultures for MAC were performed.

There were no significant survival differences between the subjects receiving rifabutin and those receiving placebo during the study period. Bacteremia, which was the primary study endpoint, occurred in the control group in 17.6 percent of patients at a median CD4+ count of 12 cells/μL and in the rifabutin group in 8.5 percent of patients with a median CD4+ count of 15 cells/μL. These differences in occurrence of bacteremia were significant ($P < 0.001$). No benefit was found in patients with CD4+ counts greater than 100 cells/μL at entry. Fewer treated patients than untreated control patients required hospitalization (32 percent versus 38 percent) or developed fever (29 percent versus 37 percent), fatigue (32 percent versus 38 percent), anemia (46 percent versus 53 percent), or alkaline phosphatase elevation (20 percent versus 27 percent). There were no significant differences in the incidence of weight loss, night sweats, abdominal pain, or diarrhea or in the Karnofsky performance score. Rifabutin was generally well tolerated; treatment was discontinued because of adverse events in 16 percent of the rifabutin group and 8 percent of the placebo group. Based on these findings, the Public Health Service Task Force formally recommended rifabutin prophylaxis for all patients with CD4+ lymphocyte counts of fewer than 100 cells/μL.

Limitations of the Data for Primary Care Decisions

For the clinician, the new data and recommendations based on this short-term (7-month) study need to be put into a primary care context to be useful for clinical decision making. Benefits and risks of rifabutin prophylaxis beyond 7 months are unknown. It is helpful to point out some of the weaknesses in the current studies. The rifabutin group had a higher mean base-line CD4+ level than the control group (63.5 CD4+ cells/μL versus 55.5 cells/μL). This 8-cell/μL difference correlates with about 1 month's progression of HIV disease. In advanced HIV disease, numerous complications can occur within a 1-month period. This 8-cell/μL difference might explain some of the reported findings but cannot account for all the benefits observed. The 9 percent difference in the incidence of bacteremia in the rifabutin group appears to demonstrate the ability of rifabutin to suppress MAC bacteremia; 91 percent of patients, therefore, will need to be treated to prevent the 9 percent from developing bacteremia. A similar percentage of patients would need to be treated to prevent symptoms or reduce hospitalization. Adverse events resulted in discontinuation of rifabutin in 8 percent more patients in the treated group. The effects of treatment on drug-drug interactions and patient compliance were not described but are especially important because of the complex drug regimens most patients with advanced disease require.

Evaluation before Initiating MAC Prophylaxis

Concern that chronic rifabutin treatment could induce rifampin resistance makes it mandatory that *M. tuberculosis* infection[7] be excluded by tuberculin skin testing[8] and chest radiograph before initiating rifabutin prophylaxis. We do not recommend a routine preprophylaxis mycobacterial blood culture. This approach is consistent with other prophylactic strategies, such as initiating *Pneumocystis carinii* prophylaxis without obtaining sputum evaluation. Some patients and their providers, however, might choose to obtain a mycobacterial culture. Liver function tests and a complete blood count should be obtained to evaluate possible active MAC disease and potential drug toxicity.

Rifabutin

Rifabutin (Mycobutin), formerly ansamycin, is a semisynthetic rifamycin antibiotic that is struc-

turally similar to rifampin but might be better tolerated and exhibit fewer drug interactions than rifampin. Rifabutin is approved by the Food and Drug Administration (FDA) for prophylaxis against MAC infection. Rifabutin is also active against other mycobacterial species, including *M. tuberculosis*, *M. kansasii*, and *M. marinum*. The mechanism of action of rifabutin is unclear.

Rifabutin is rapidly absorbed and has an oral bioavailabilty of 12 to 20 percent.[9] Absorption is unaffected by the presence of food. The drug undergoes hepatic metabolism by means of oxidation and deacetylation and is excreted in urine, bile, and feces. About 10 percent of the drug is excreted unchanged in the urine. The terminal half-life ranges from 36 to 46 hours. Rifabutin is extensively distributed into body tissues. The cerebrospinal fluid concentrations are about one-half those of serum concentrations.[10]

At dosages less than 1 g daily, rifabutin is generally well tolerated. Side effects similar to those caused by rifampin can be expected. Gastrointestinal distress (primarily nausea) and rash are most common. Uncommon toxicities include neutropenia; thrombocytopenia; anemia; a flulike syndrome characterized by fever, myalgias, and headache; elevated transaminase levels; hepatitis; arthritis; arthralgias at dosages greater than 1 g/d[11]; loss of sense of taste (ageusia)[12]; myositis; renal impairment; and chest pain with dyspnea. Adverse effects are reported most often when dosages of rifabutin exceed 450 mg daily. Prophylaxic dosages of 300 mg daily or 150 mg twice daily appear to be better tolerated. In the current clinical trials, adverse effects leading to rifabutin discontinuation occurred in 16 percent of patients.[2] Because adverse effects of rifabutin are similar to those of rifampin, patients should be alerted that a brown-orange discoloration of bodily secretions (including permanent staining of contact lenses) and skin pigmentation can occur. Rifabutin should be avoided by patients who experience hypersensitivity or adverse reactions to rifampin, as cross-sensitivity is likely. Use of rifabutin to prevent MAC disease might contribute to the development of multiresistant strains of *M. tuberculosis*.

Rifabutin might be less likely than rifampin to cause marked drug interactions because it does not appear to interact with the cytochrome P-450 system as much as rifampin. Rifampin is a potent hepatic enzyme inducer of the cytochrome P-450 system that can decrease the effectiveness of many drugs used in the management of HIV disease. Rifampin can increase metabolism of methadone, ketoconazole, fluconazole, itraconazole, corticosteroids, and oral contraceptives so that higher dosages are often required to maintain efficacy.[13] Nevertheless, rifabutin does induce its own metabolism[10,14]; therefore, the potential for drug interactions should be expected. In one study, rifabutin produced a 25 percent reduction in antipyrine half life, compared with a 40 percent reduction with rifampin.[15] Of patients receiving methadone maintenance, symptoms of narcotic withdrawal occurred in 18 percent after rifabutin administration and in 80 percent receiving rifampin.[16] Preliminary studies have indicated that isoniazid,[14] didanosine, and fluconazole metabolism are not changed after rifabutin administration. The area under the curve (a measurement of the amount of drug in blood in a 24-hour period) of zidovudine is decreased 32 percent by rifabutin administration; the clinical importance of this measurement is unknown.[17] Rifabutin, therefore, appears similar to rifampin but might be better tolerated and exhibit fewer drug interactions.

Pharmacy acquisition cost of rifabutin at the recommended 300-mg daily dosage for MAC prophylaxis is approximately $2000 to $2400 per year per patient. Rifabutin can be given as one 300-mg dose or as 150 mg twice daily to minimize gastrointestinal distress. Dosage adjustment might be indicated in severe hepatic or renal insufficiency. Clinical trials of alternative prophylactic agents, such as clarithromycin and azithromycin for patients unable to take rifabutin, are now in progress.

Recommendations

The decision to initiate MAC prophylaxis should be a joint one, with the patient, the family, and the primary provider discussing the risks, benefits, and costs of the different approaches. When survival benefit is not expected, as is the case with rifabutin prophylaxis against MAC disease, symptomatic benefits should exceed the risks to justify prophylaxis. The potential benefits of preventing bacteremia (9 percent difference between treated and untreated patients), as well as

preventing hospitalization and selected symptoms (up to 8 percent difference), will need to be balanced against potential drug toxicity (8 percent difference). There are no available data that compare MAC prophylaxis with the strategy of no prophylaxis and treating acute disease. Nevertheless, because rifabutin prophylaxis is generally well tolerated, its use in advanced disease is appropriate.

We recommend offering rifabutin to patients without symptomatic MAC disease when the CD4+ lymphocyte count decreases to fewer than 50 cells/μL. Patients expressing a preference for earlier treatment can receive rifabutin after the CD4+ count decreases to fewer than 100 cells/μL. These recommendations are consistent with San Francisco General Hospital guidelines for MAC prophylaxis. Although a national panel has formally recommended rifabutin for patients with fewer than 100 CD4+ cells/μL, we do not believe the present data are strong enough to consider rifabutin prophylaxis a requirement of HIV primary care at that CD4+ level. Patients who are either unable to tolerate or do not wish to receive MAC prophylaxis should be reassured that they are not receiving inadequate care as long as careful monitoring for symptomatic MAC disease is part of their primary care.

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References

1. Horsburgh CR Jr. *Mycobacterium avium* complex infection in the acquired immunodeficiency syndrome. N Engl J Med 1991; 324:1332-8.
2. Nightingale SD, Cameron DW, Gordin FM, Sullam PM, Cohn DL, Chaisson RE, et al. Two controlled trials of rifabutin prophylaxis against *Mycobacterium avium* complex infection in AIDS. N Engl J Med 1993; 329:828-33.
3. Masur H. Recommendations on prophylaxis and therapy for disseminated *Mycobacterium avium* complex disease in patients infected with the human immunodeficiency virus. Public Health Service Task Force on Prophylaxis and Therapy for *Mycobacterium Avium* Complex. N Engl J Med 1993; 329: 898-904.
4. US Public Health Service Task Force on Prophylaxis and Therapy for *Mycobacterium avium* Complex. Recommendations on prophylaxis and therapy for disseminated *Mycobacterium avium* complex for adults and adolescents infected with human immunodeficiency virus. MMWR 1993; 42 (RR-9):14-20.
5. Nightingale SC, Byrd LT, Southern PM, Jockusch JD, Cal SX, Wynne BA. Incidence of *Mycobacterium avium-intracellulare* complex bacteremia in human immunodeficiency virus-positive patients. J Infect Dis 1992; 165:1082-5.
6. Goldschmidt RH, Dong BJ. Treatment of AIDS and HIV-related conditions — 1993. J Am Board Fam Pract 1993; 6:297-316.
7. Barnes PF, Bloch AB, Davidson PT, Snider DE Jr. Tuberculosis in patients with human immunodeficiency virus infection. N Engl J Med 1991; 324: 1644-50.
8. Purified protein derivative (PPD)-tuberculin anergy and HIV infection: guidelines for anergy testing and management of anergic persons at risk of tuberculosis. MMWR 1991; 40(RR-5):27-33.
9. Narang PK, Lewis RC, Bianchine JR. Rifabutin absorption in humans: relative bioavailability and food effect. Clin Pharmacol Ther 1992; 52:335-41.
10. Skinner MH, Hsieh M, Torseth J, Pauloin D, Bhatia G, Harkonen S, et al. Pharmacokinetics of rifabutin. Antimicrob Agents Chemother 1989; 33:1237-41.
11. Siegal FP, Eilbott D, Burger H, Gehan K, Davidson B, Kaell AT, et al. Dose-limiting toxicity of rifabutin in AIDS-related complex: syndrome of arthralgia/arthritis. AIDS 1990; 4:433-41.
12. Morris JT, Kelly JW. Rifabutin-induced ageusia [letter]. Ann Intern Med 1993; 119:171-2.
13. Borcherding SM, Baciewicz AM, Self TH. Update on rifampin drug interactions. Arch Intern Med 1992; 152:711-6.
14. Breda M, Pianezzola E, Strolin-Benedetti M, Efthymiopoulos C, Carpentieri M, Sassella D, et al. A study of the effects of rifabutin on isoniazid pharmacokinetics and metabolism in healthy volunteers. Drug Metabol Drug Interact 1992; 10:323-40.
15. Perucca E, Grimaldi R, Frigo GM, Sardi A, Mönig H, Ohnhaus EE. Comparative effects of rifabutin and rifampicin on hepatic microsomal enzyme activity in normal subjects. Eur J Clin Pharmacol 1988; 34:595-9.
16. Sawyer RC, Brown LS, Narang PK, Li R. Evaluation of possible pharmacologic interaction between rifabutin (RIF) and methadone (MET) in HIV (+) injecting drug users (IDUs). Presented at the Ninth International Conference on AIDS, Berlin, June 6-11, 1993. Abstract.
17. Narang P, Nightingale S, Manzone C, Colborn D, Wynne B, Li R, et al. Does rifabutin (RIF) affect zidovudine (ZDV) disposition in HIV (+) patients? Presented at the Eighth International Conference on AIDS, Amsterdam, July 19-24, 1992. Abstract.