Rifabutin Therapy for Disseminated *Mycobacterium avium* Complex Infection

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Although numerous antimicrobial agents have been used to treat disseminated *Mycobacterium avium* complex (MAC) infection, the optimal therapy for this disease is unknown. One potentially effective agent is rifabutin, which has demonstrated activity against MAC both in vitro and in animal models of infection. In clinical trials, cultures of blood from 46% to 92% of patients become sterile after therapy with rifabutin combined with ethambutol, clofazimine, or amikacin. Moreover, the efficacy of ethambutol combined with clofazimine is markedly enhanced by rifabutin. In combination with clarithromycin, rifabutin at dosages of ≥450 mg/d has been associated with a high incidence of uveitis, thus indicating that only 300 mg/d may be given with this macrolide. Although a definitive role for rifabutin in the treatment of MAC infection has not been established, this agent will likely be of value as an adjunct to macrolide-based therapy or in the treatment of macrolide-intolerant patients.

*Mycobacterium avium* complex (MAC) has long been recognized as a frequent cause of chronic pulmonary infection, especially in patients with underlying medical conditions such as silicosis [1]. Until recently disseminated infection was rare; only about three dozen cases were reported in the pre-AIDS era [2]. In 1981, however, numerous centers began to observe cases of MAC bacteremia and multiorgan involvement in patients with AIDS [3]. At first there was controversy as to whether infection with this organism represented true disease or merely colonization. Subsequent case-control studies have demonstrated that patients with disseminated MAC infection are more likely to be symptomatic with fever, chills, wasting, and diarrhea. Moreover, disseminated MAC infection is associated with a 50% reduction in life expectancy [4–7] (figure 1).

In view of these findings, most authorities recommend antimicrobial therapy for all patients with disseminated MAC infection [8–10]. The agents proposed for therapeutic use include macrolides, rifamycins, quinolones, clofazimine, ethambutol, and amikacin. However, the optimal treatment of disseminated MAC infection has not yet been clearly determined. Most trials have examined the efficacy of one or more multidrug regimens, each typically containing three or four agents. As a result it is difficult to quantify the contribution of any single drug in clearing infection. Although a few studies have assessed the efficacy of monotherapy with individual antimicrobial agents [11, 12], thus providing some data on the relative efficacy, no such information exists for rifabutin. Despite these limitations, results from in vitro studies, animal models of infection, and clinical trials indicate that rifabutin may be of value as therapy for disseminated MAC infection.

**In Vitro Studies**

Since the in vitro activity of rifabutin is addressed elsewhere in this supplement, details of such data will not be discussed at length here. In brief, several studies indicate that, as measured by MICs, rifabutin is active against MAC in vitro. Although MICs vary considerably between strains and with differing methodologies, MIC₉₀ values of 0.1 to 0.5 μg/mL are typical, as are MIC₉₀ values of 0.5 to 4.0 μg/mL [13, 14]. Given that oral administration of rifabutin results in peak serum concentrations of 0.4 to 0.6 μg/mL [15], 20%–32% of strains have been classified as "susceptible;" another 57%–74% have been deemed "moderately susceptible." Although the above MICs are at best only minimally lower than the achievable serum levels of this drug, concentrations of rifabutin within macrophages are severalfold higher, possibly rendering this agent more effective in killing intracellular organisms [16].

In addition to its intrinsic antimicrobial activity, synergy in vitro between rifabutin and a variety of other agents (including ethambutol and clarithromycin) has also been reported [17, 18], further suggesting that rifabutin may be of value as therapy. Numerous questions exist about the validity of in vitro assays for antitubercular activity. These methods are not standardized, and results often vary under different experimental conditions. Notwithstanding these caveats, such data have provided the rationale for subsequent testing in animal models of infection and in humans.

**In Vivo Studies**

Additional evidence for the activity of rifabutin is provided by animal models of disseminated MAC infection. In studies by Gangadharam et al. [19, 20], beige mice infected with MAC had little response to rifabutin alone. However, combinations of rifabutin with clofazimine were more effective than the latter drug alone in reducing titers of MAC organisms within the
that this agent may be of value in the treatment of humans. Table 1. Response of patients with MAC organisms within organs of infected animals indicates above-mentioned studies, the ability of rifabutin to reduce titers producing immunosuppression. Nonetheless, in most of the MAC infection was reported by Masur et al. [27], who treated patients with AIDS and MAC bacteremia with rifabutin (150 mg/d) and clofazimine, often in combination with amikacin. Although these studies indicate that regimens containing rifabutin may be effective in the treatment of disseminated MAC infection, the relative contribution of rifabutin in reducing microbial titers cannot be determined since other agents were used concurrently. However, the impact of rifabutin on therapeutic response is addressed in a recent double-blind, placebo-controlled, randomized trial [30] that examined the efficacy of ethambutol and clofazimine combined with either rifabutin (600 mg/d) or placebo as treatment of patients with AIDS and MAC bacteremia. The primary endpoint was microbiological response, defined as sterilization or at least a 2 log₁₀ reduction in cfu/mL of blood. By week 4 of treatment, seven of 11 patients in the rifabutin group were classified as responders, as compared with none of 13 patients in the placebo group (P < .001) (table 1). Similar results were seen at weeks 8 and 12 of treatment. Cultures of blood from all but one responder became sterile. No significant differences were noted between the two groups in terms of adverse effects.

Taken as a whole, the above-mentioned studies indicate that rifabutin has activity against disseminated MAC infection in humans and that rifabutin in combination with other agents would prove effective as therapy for MAC infection. It should be noted that the response rates noted above are better than those reported for many non-macrolide-containing regimens [31, 32]. However, trials with macrolides have shown even greater efficacy. For example, Dautzenberg et al. [33] have reported a 63%–98% rate of sterilization of cultures of blood from patients receiving a clarithromycin-containing regimen. Comparable response rates have also been noted by Chaisson et al. [34] for clarithromycin monotherapy and by Young et

As with the in vitro studies discussed above, results from animal studies have not been wholly consistent. Because of differences among strains of MAC used in these models (in terms of both virulence and antimicrobial susceptibility), there exists an enormous potential for experimental artifact. Other variables include differences in susceptibility to MAC among mice or rat species and, in some models, different methods of producing immunosuppression. Nonetheless, in most of the above-mentioned studies, the ability of rifabutin to reduce titers of MAC organisms within organs of infected animals indicates that this agent may be of value in the treatment of humans.

### Clinical Studies

One of the earliest experiences with rifabutin as therapy for MAC infection was reported by Masur et al. [27], who treated patients with AIDS and MAC bacteremia with rifabutin (150 mg/d) and clofazimine, often in combination with amikacin. Cultures of blood from six of 13 evaluable patients became sterile. However, clinical improvement was noted in only one case. In a subsequent study by Hoy et al. [28], cultures of blood from 22 of 25 patients became sterile (mean time to sterilization, 6.5 weeks) following therapy with rifabutin (300 mg/d) combined with isoniazid, ethambutol, and clofazimine. Clinical improvement in several MAC-related symptoms and signs was noted at 3 months. Similar results were observed by Dautzenberg et al. [29], who used a regimen of rifabutin (300–600 mg/d), isoniazid (5 mg/[kg· d]), and clofazimine (100 mg/ d). Cultures of blood from 16 of 23 patients for whom bacteriologic data were available became sterile by the third month of treatment. However, of those 16 responders, four (25%) eventually relapsed.

### Table 1. Response of patients with Mycobacterium avium complex bacteremia to treatment with rifabutin or placebo in combination with clofazimine and ethambutol.

<table>
<thead>
<tr>
<th>Week of therapy</th>
<th>No. of patients with microbiological response/total no. of patients evaluated*</th>
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<tbody>
<tr>
<td>4</td>
<td>RBT/CLO/EMB: 7/11 vs. PLA/CLO/EMB: 0/13, P &lt; .001</td>
</tr>
<tr>
<td>8</td>
<td>RBT/CLO/EMB: 7/10 vs. PLA/CLO/EMB: 1/8, P = .025</td>
</tr>
<tr>
<td>12</td>
<td>RBT/CLO/EMB: 6/9 vs. PLA/CLO/EMB: 1/7, P = .060</td>
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NOTE. RBT = rifabutin; CLO = clofazimine; EMB = ethambutol; PLA = placebo. Reprinted with permission from [30].

* For all responders in both groups, blood cultures were sterile, except for one patient receiving RBT/CLO/EMB (at week 4 a 2 log₁₀ reduction in cfu/mL of blood was noted).
al. [35] for azithromycin monotherapy. On the basis of such data, the U.S. Public Health Service has recommended that all patients with AIDS and disseminated MAC infection be treated with macrolides (either clarithromycin or azithromycin), usually in combination with ethambutol and possibly a third agent [10].

Current Studies

In view of these recommendations, most ongoing trials on the treatment of MAC infection in North America have at least one treatment arm containing a macrolide. Among the studies examining the efficacy of rifabutin is Pharmacia 0250. This double-blind, randomized, three-arm trial initially compared two doses of rifabutin (900 or 600 mg/d) or placebo combined with clarithromycin (1,000 mg b.i.d.) and ethambutol (15 mg/[kg·d]). Enrollment began in April 1993 at about 40 centers throughout the United States.

Two subsequent developments have necessitated modification of the protocol. In reviewing data on clarithromycin monotherapy for MAC infection, the Food and Drug Administration (FDA) noted an increased mortality rate among patients receiving 1 g b.i.d. Although no reason for this association was apparent, the FDA recommended that the maximum dose be reduced to 500 mg b.i.d. for these patients [10]. In addition, by late 1993 reports began to emerge of uveitis in patients receiving therapy with rifabutin in combination with clarithromycin. The Canadian HIV Trials Network Study 087174 (discussed below) noted that 23 (39%) of 59 patients given 600 mg/d of rifabutin combined with 1 g of clarithromycin (plus ethambutol) b.i.d. had uveitis [36]. Concurrently, nine of the 65 patients in the Pharmacia 250 trial had uveitis (B. Wynne [Pharmacia, Piscataway, NJ], personal communication). Since this study remains blinded, the precise incidence of uveitis in each treatment arm cannot be determined. Estimates range from 13.8% (if cases were equally distributed among the three arms) to 39.1% (if all cases were in a single arm).

The possible mechanisms of this toxic effect are discussed elsewhere in this supplement. It is likely, however, that the pathogenesis of uveitis is related to the pharmacokinetic interaction of clarithromycin and rifabutin. By inhibiting the cytochrome P-450 pathway, clarithromycin reduces the metabolism of rifabutin, thus resulting in increased serum and tissue concentrations [37, 38]. It is presumed that these high levels of rifabutin are cytotoxic or promote inflammation, but the details of this process remain undefined.

In view of these reports of uveitis, the protocol for the Pharmacia 0250 study was modified in December 1993. The dosage of clarithromycin was reduced to 500 mg b.i.d., and that of rifabutin was reduced to either 450 or 300 mg/d. During the subsequent 6 months, four additional cases of uveitis were described in 102 new enrollees. On the basis of the recommendations of the Data Safety Monitoring Board for this study, the 450-mg treatment arm was discontinued. Thus, Pharmacia 0250 is now a two-arm trial comparing 300 mg of rifabutin or placebo in combination with clarithromycin and ethambutol. Completion of enrollment is anticipated by the end of 1995.

Several other trials that include rifabutin for the treatment of MAC infection are currently in progress or scheduled to start. The Canadian HIV Trials Network Study 087174 is an open-label, two-arm, prospective study comparing rifampin (600 mg/d), ethambutol (15 mg/[kg·d]), ciprofloxacin (750 mg b.i.d.), and clofazimine (100 mg/d) with rifabutin (600 mg/d), ethambutol (15 mg/[kg·d]), and clarithromycin (1 g b.i.d.). The two regimens will be assessed with respect to microbiological response (defined as two or more sterile blood cultures at week 16 of therapy), clinical response, and survival. Because of the cases of uveitis discussed above, the dose of rifabutin has been reduced from 600 to 300 mg/d. Enrollment began in October 1992, with a goal of enrolling 200 patients by early 1995.

ACTG 223 is a three-arm, prospective study comparing clarithromycin (500 mg b.i.d.) combined with ethambutol, rifabutin (450 mg/d), or both. Patients will be randomized to one of the above-mentioned regimens and monitored every 4 weeks for clinical and microbiological responses. Patients with a significant reduction in titers will continue their treatment, while those lacking such a response will be randomized to a salvage regimen. Recruitment is scheduled to begin in 1995, with a target number of 246 enrollees.

CPCRA 027 is a prospective, four-arm study comparing clarithromycin (500 or 1,000 mg/d) and ethambutol combined with either rifabutin (450 mg/d) or clofazimine. The endpoints are microbiological response (defined as sterile blood cultures after 2 months of therapy), clinical response, and survival. A total of 400 patients will be enrolled over a period of 2 years beginning in 1995.

Summary

Numerous studies, either in progress or planned, will help define the role of rifabutin in the treatment of disseminated MAC infection. Pending the results of these trials, several roles may be postulated for this agent. First, rifabutin may be of value as part of a macrolide-containing regimen as initial therapy for MAC infection. When used in conjunction with macrolides, rifabutin may either enhance the rate of clearance of MAC or prevent the emergence of resistance. Clearly, the risk of uveitis must be considered if rifabutin is to be used with macrolides. However, rifabutin at dosages of 300 mg/d (or even 150 mg/d) may result in a low (but still detectable [39]) incidence of uveitis while still contributing to the antimicrobial activity of macrolide regimens. As an alternative approach, rifabutin could be used during the initial 4–8 weeks of clarithromycin therapy, with the goal of inducing a more rapid reduction in titers of MAC organisms or a more prompt clinical improvement. Combination therapy of such limited duration may be associated with a lower incidence of uveitis than has been observed with more prolonged treatment.
Another therapeutic option would be rifabutin in combination with azithromycin. The pharmacokinetic interactions between rifabutin and azithromycin are likely to be considerably less than those seen with clarithromycin, since azithromycin does not inhibit the cytochrome P-450 pathway [38]. Thus, regimens containing azithromycin and rifabutin may incur a smaller risk of toxicity.

Rifabutin may also be a useful alternative to macrolides. As discussed above, combining rifabutin with ethambutol and clofazimine resulted in a microbiological response in most patients. This finding suggests that such regimens would be of value as initial therapy for patients intolerant of macrolides or, alternatively, as maintenance therapy for patients who initially respond to macrolides but who become intolerant of these agents.

In addition to defining the clinical efficacy of rifabutin, future trials will need to examine several related therapeutic issues. For example, it is unknown if rifabutin is less active in patients who have disseminated MAC infection while receiving rifabutin prophylaxis. Although emergence of resistance was not detected in the two large prophylaxis trials (Adria 023 and 027), these studies did not address the therapeutic response of patients for whom rifabutin prophylaxis had failed [40]. Other issues include the impact of rifabutin on the pharmacokinetics of other drugs and the effects of rifabutin therapy for MAC infection on resistance among other mycobacterial species. These and related questions await resolution by pending studies.

Addendum

Several developments relating to current studies discussed in this paper have recently occurred. Pharmacia 0250 has completed enrollment of new patients; preliminary results are anticipated by the end of 1996. Final data from the Canadian HIV Trials Network Study 087174 were presented last fall, indicating that combination therapy with rifabutin, clarithromycin, and ethambutol results in higher rates of microbial clearance from the blood (67 [69%] of 97 patients) than does the four-drug regimen (29 [30%] of 90 patients) [41]. The response rate was dependent on the dosage of rifabutin and was higher at 600 mg/d (79%) than at 300 mg/d (58%). However, the higher dosage was frequently associated with the development of uveitis (24 of 62 patients), which was not the case with the lower dosage (3 of 54). ACTG 223 and CPCRA 027 have begun enrollment; no results are currently available.

References

3. Havlik JA Jr, Horsburgh CR Jr, Metchock B, Williams PP, Fann SA, Thompson SE III. Disseminated Mycobacterium avium complex infec-

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Discussion

DR. MICHAEL TAPPER. Wasn't there a question about compliance in the high-dose arm of your trial of clarithromycin for treatment of Mycobacterium avium complex (MAC) infection?

DR. RICHARD E. CHAISSON. No, if you look at the results of that study (ACTG [AIDS Clinical Trials Group] 157), the mortality at 12 weeks among patients in the 500-mg arm was 3%; among those in the 1-g and 2-g arms, mortality was 14%–15%. A time-to-death analysis showed that there was a significant difference between the low-dose and high-dose groups in terms of mortality; there was no way to eliminate that difference. What this mortality difference means is not made clear by the U.S. Food and Drug Administration label for clarithromycin for treatment of MAC infections; it actually says that the reason for increased mortality is not known.

There are many speculations about this increased mortality. One is that higher doses are lethal; another is that patients in the low-dose arm were heartier and had better Karnofsky scores. There are many possible reasons, but currently nobody knows, or will ever know, why there was a higher mortality associated with the higher doses in our trial. It's an important question because Dr. Bertrand Dautzenberg has shown that higher doses aren't more lethal, although they are more toxic and more microbiologically active. Whether there is a difference in mortality associated with the higher dose is an important question, which the CPCRA MAC treatment trial will address.

DR. TAPPER. How will azoles be used in this patient population? Should they be avoided?

DR. PAUL M. SULLAM. It's hard to say because the use of azoles is so ubiquitous. This question is probably less of an issue for patients receiving rifabutin but no macrolides. However, I suspect that patients who are also receiving macrolides will probably have to get a lower dose. One objective of these studies will be to fine-tune the dose.

DR. BERTRAND DAUTZENBERG. Have you submitted any data on rifabutin preventing the development of resistance to clarithromycin after 12 or 8 weeks of treatment?

DR. FRED M. GORDIN. I think, Dr. Dautzenberg, you have presented some other data on clarithromycin in various combinations that showed, if I'm correct, that ethambutol seemed to prevent the development of resistance in MAC isolates.

DR. BEVERLEY WYNNE. On the basis of a preliminary look at the data, we haven't observed any relapses in patients who have cleared mycobacteria from the blood. However, we don't have enough data at this time to answer the question. I want to comment on the European MAC treatment trials, the United States treatment trial, and the Canadian treatment trial, in which 60%–70% of patients were receiving an azole (primarily flu-
The doses of azoles varied a lot in the trials, so it's hard to say what the mean dose was.

DR. P. K. NARANG. Of the top 10 medications used, at least in the prophylaxis trials, five of them are azoles (not just fluconazole). Other azoles that can have similar inhibitory properties are being used.

DR. SULLAM. An interesting sidelight of the rifabutin prophylaxis study was just how widely azoles are used. We had discussed analyzing their use, but I think people are clearly using these drugs for prophylaxis as well as treatment; however, the evidence for their efficacy as prophylaxis is not definitive.

DR. TAPPER. It would be important to determine their efficacy, because there are significant differences in the dosages used. For example, in Europe, the dosage of fluconazole is often much lower than that commonly used in the United States. The other issue is that there are significant differences in the bioavailability of the azoles; fluconazole is more extensively absorbed than are itraconazole or ketoconazole.

DR. GORDIN. Dr. Phillips, what has happened with the Canadian trial since the complication of uveitis was reported? Have the dosages of rifabutin been changed, or are patients staying in the trial while they are being treated for uveitis?

DR. PETER PHILLIPS. The dosage of rifabutin was changed. Initially, it was 600 mg/d, and it was dropped to 300 mg/d when the association was first noted. Since then, the safety committee has conducted another review because of the development of acute cases of uveitis (now a total of three) at the lower dose of 300 mg/d within that treatment combination. However, the study continues despite these additional cases. Our approach is to stop administering rifabutin when uveitis develops, although some patients have been managed successfully by reintroducing the drug and continuing topical therapy for uveitis (that's not the approach that's being taken by the Canadian trials network). We are continuing to monitor these patients closely, and we hope that we won't see an increase in the number of cases of uveitis.

DR. DAUTZENBERG. How many patients were cured of uveitis after rifabutin was withdrawn?

DR. SULLAM. My understanding is that with recognition of inflammation and withdrawal of the drug, all patients who developed uveitis have recovered.

DR. PHILLIPS. In the Canadian study, the duration of symptomatic uveitis was longer, usually on the order of several weeks, before the association was recognized. But since this association has become well known to investigators, treatment with the drug is being stopped right away, and the duration of symptoms is much shorter—on the order of 1 or 2 weeks.

DR. TAPPER. Could you speculate a bit more about a subject you touched on: the role of drugs in terms of both induction therapy and maintenance therapy? Some drugs, such as amikacin, come to mind as being rather useful as induction therapy or perhaps as reinduction therapy after relapse, but perhaps not for long-term maintenance therapy. What is the future of therapy for MAC disease?

DR. SULLAM. I think tuberculosis, or perhaps more-conventional bacterial infections, is a model. Phase 1 is a regimen that can produce either enduring suppression or sterilization; phase 2 is one of more rapid response. One problem with the early trials for MAC infection was that it would take many weeks to get a response. With application of some of the newer drugs such as macrolides and rifabutin, it's possible to achieve the first phase of treatment. Time to sterilization is shortened to 2 weeks, instead of 6 or 8 weeks. That shorter duration may seem trivial, but for a patient whose life expectancy would otherwise be 4 or 6 months, it is significant. It could also have an impact on survival because the wasting syndrome associated with MAC infection is arrested. I see phase 2 as one of adjusting regimens to effect prompt and lasting sterilization, with a third phase consisting of simpler, safer regimens and compliance.

DR. TERRENCE F. BLASCHKE. Given the appropriate concern about the variety of possible drug interactions and given that, even without drug interactions, there may be substantial variability in the disposition of these drugs, particularly those that are metabolized, I hope that some thought is being given to taking advantage of the situation to monitor the patients who develop toxicity and to determine serum concentrations of the drugs so that we can establish whether the interactions themselves are in fact contributing to the incidence of the toxicities, whether they be uveitis or any other toxicities.

DR. SULLAM. In the studies I've been involved with, such as Pharmacia 065 and Pharmacia 250, the pharmacokinetics and serum levels of the drugs are part of the analysis.