A Prospective, Randomized Trial Examining the Efficacy and Safety of Clarithromycin in Combination with Ethambutol, Rifabutin, or Both for the Treatment of Disseminated *Mycobacterium avium* Complex Disease in Persons with Acquired Immunodeficiency Syndrome

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This multicenter, randomized, open-label phase 3 clinical trial compared the safety and efficacy of 3 clarithromycin-containing combination regimens for the treatment of disseminated *Mycobacterium avium* complex (MAC) disease in persons with acquired immunodeficiency syndrome. A total of 160 eligible patients with bacteremic MAC disease were randomized to receive clarithromycin with either ethambutol (C+E), rifabutin (C+R), or both (C+E+R) for 48 weeks. After 12 weeks of treatment, the proportion of subjects with a complete microbiologic response was not statistically significantly different among treatment arms: the proportion was 40% in the C+E group, 42% in the C+R group, and 51% in the C+E+R group ($P = 0.454$). The proportion of patients with complete or partial responses who experienced a relapse while receiving C+R (24%) was significantly higher than that of patients receiving C+E+R (7%; $P = 0.027$). Subjects in the C+E+R group had improved survival, compared with the C+E group (hazard ratio [HR], 0.44; 95% confidence interval [CI], 0.23–0.83) and the C+R group (HR, 0.49; 95% CI, 0.26–0.92).

Disseminated disease due to *Mycobacterium avium* complex (MAC) has been among the most common serious opportunistic infections occurring in persons with HIV-1 infection and advanced immunosuppression [1–8]. Since 1995, the incidence of MAC disease has decreased dramatically, to an estimated 1–3 cases/100 patient-years, coincident with widespread use of both MAC prophylaxis and potent antiretroviral therapies [9–13]. However, HIV-infected individuals with advanced immunosuppression who are not receiving or are unable to tolerate antiretroviral regimens...
Table 1. Selected baseline characteristics and laboratory values for patients with AIDS who received combination clarithromycin therapy for *Mycobacterium avium* complex (MAC) disease, by treatment arm.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total (n = 160)</th>
<th>C+E (n = 53)</th>
<th>C+R (n = 50)</th>
<th>C+E+R (n = 57)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>139 (87)</td>
<td>43 (81)</td>
<td>44 (88)</td>
<td>52 (91)</td>
</tr>
<tr>
<td>Female</td>
<td>21 (13)</td>
<td>10 (19)</td>
<td>6 (12)</td>
<td>5 (9)</td>
</tr>
<tr>
<td>Race/ethnicity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>56 (35)</td>
<td>21 (40)</td>
<td>17 (34)</td>
<td>18 (32)</td>
</tr>
<tr>
<td>African American</td>
<td>74 (46)</td>
<td>24 (45)</td>
<td>23 (46)</td>
<td>27 (47)</td>
</tr>
<tr>
<td>Latino</td>
<td>24 (15)</td>
<td>8 (15)</td>
<td>9 (18)</td>
<td>7 (12)</td>
</tr>
<tr>
<td>Other</td>
<td>6 (4)</td>
<td>0 (0)</td>
<td>1 (2)</td>
<td>5 (9)</td>
</tr>
<tr>
<td>Current/previous injection drug use</td>
<td>36 (23)</td>
<td>8 (15)</td>
<td>13 (26)</td>
<td>15 (26)</td>
</tr>
<tr>
<td>Protease inhibitor use</td>
<td>23 (14)</td>
<td>8 (15)</td>
<td>6 (12)</td>
<td>9 (16)</td>
</tr>
<tr>
<td>Age, median years (range)</td>
<td>36 (20–55)</td>
<td>35 (27–47)</td>
<td>35 (25–55)</td>
<td>37 (20–47)</td>
</tr>
<tr>
<td>Karnofsky score, median (range)</td>
<td>70 (30–100)</td>
<td>70 (40–100)</td>
<td>70 (30–100)</td>
<td>70 (30–90)</td>
</tr>
<tr>
<td>Median laboratory value (range)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD4+ cell count, cells/μL</td>
<td>8 (0–408)</td>
<td>9 (0–89)</td>
<td>9 (0–63)</td>
<td>7 (0–408)</td>
</tr>
<tr>
<td>MAC bacteremia level, log10 cfu/mL</td>
<td>1.623 (0–7.228)</td>
<td>1.696 (0–7.228)</td>
<td>1.628 (0–6.909)</td>
<td>1.554 (0–5.35)</td>
</tr>
<tr>
<td>SGOT/AST level, IU/L</td>
<td>41 (10–371)</td>
<td>40 (15–189)</td>
<td>41 (13–371)</td>
<td>41 (10–309)</td>
</tr>
<tr>
<td>Alkaline phosphatase level, IU/L</td>
<td>127 (48–1805)</td>
<td>118 (50–1341)</td>
<td>135 (48–1805)</td>
<td>133 (60–1493)</td>
</tr>
<tr>
<td>SGPT/ALT level, IU/L</td>
<td>33 (6–160)</td>
<td>33 (8–128)</td>
<td>35 (8–157)</td>
<td>30 (6–160)</td>
</tr>
<tr>
<td>Hemoglobin concentration, g/dL</td>
<td>9.5 (5.3–14.6)</td>
<td>9.0 (6.3–12.0)</td>
<td>9.6 (5.2–14.4)</td>
<td>9.8 (5.3–14.6)</td>
</tr>
</tbody>
</table>

NOTE. Data are no. (%) of patients, unless otherwise indicated. ALT, alanine aminotransferase; AST, aspartate aminotransferase; C, clarithromycin; E, ethambutol; R, rifabutin; SGOT, serum glutamic oxaloacetic transaminase; SGPT, serum glutamic pyruvic transaminase.

* No statistically significant differences were detected among the treatment arms for any baseline characteristic.

continue to develop disseminated MAC disease.

Published recommendations for treating disseminated MAC disease state that at least 2 antimycobacterial drugs active against MAC should be used to reduce the potential that antibiotic resistance will develop [8, 13]. Either clarithromycin or azithromycin is recommended as the first agent; ethambutol is the recommended second drug [8, 13]. For severe cases, some suggest adding rifabutin, ciprofloxacin, amikacin, or another antimycobacterial drug [8, 13]. In previous studies, macrolide-based therapy of disseminated MAC disease has resulted in improvement of symptoms, clearance of mycobacteremia, and prolonged survival, but relapse due to resistant organisms was common [14–23]. Although macrolides are recognized to be the most active of the drugs available for treatment of MAC disease, several important questions remain in defining optimal treatment. Namely, it remains critical to evaluate the contribution of any single additional drug versus 2 drugs to macrolide-containing combination regimens with respect to the rate of relapse, emergence of resistance, and survival. This study was undertaken to compare the contribution of ethambutol, rifabutin, or both when added to clarithromycin for the treatment of disseminated MAC disease in persons with AIDS.

**METHODS**

**Study population and study design.** This open-label, phase 3 study compared the safety and efficacy of 3 clarithromycin-containing regimens for the treatment of disseminated MAC disease in AIDS patients. Subjects were recruited from 21 sites of the National Institute of Allergy and Infectious Diseases (NIAID) Adult AIDS Clinical Trials Group. This protocol was approved by the institutional review board at each participating site, and each subject gave written informed consent before enrollment. The human experimentation guidelines of the US Department of Health and Human Services and local institutional review boards were followed at all participating sites.

HIV-infected subjects were eligible if they were at least 13 years old, had a Karnofsky performance score of ≥30, had stable condition while receiving therapy for any infectious processes other than MAC infection, had received at most 14 days of antimycobacterial therapy within the 30 days before study entry, and had either (1) symptoms of MAC disease and 1 culture of blood or a specimen from a normally sterile body site positive for MAC or acid-fast bacilli or (2) no symptoms but 2 blood cultures obtained at least 24 h apart that were positive for MAC or acid-fast bacilli. Subjects were excluded if
they were pregnant or lactating, had active mycobacterial infection caused by microorganisms other than MAC that required treatment, or had life expectancy of <8 weeks. Because of the time required to detect MAC in blood cultures, subjects were enrolled pending baseline culture results. However, those with negative results of baseline culture were considered ineligible, their study participation was discontinued, and they were followed up for survival only.

Subjects were randomized in equal proportions to receive either clarithromycin (500 mg twice daily) and ethambutol (15 mg/kg once daily; C+E), clarithromycin (500 mg twice daily) and rifabutin (450 mg once daily; C+R), or a combination of clarithromycin, ethambutol, and rifabutin in the same dosages (C+E+R). After protease inhibitors (PIs) became available, the protocol was amended to decrease rifabutin dosages to 150 mg/day for subjects receiving indinavir or nelfinavir and to 150 mg every other day for those receiving ritonavir.

Subjects were evaluated for symptoms of MAC disease, adverse events, and adherence to the drug regimens, and a blood sample for culture for MAC was obtained at baseline; at weeks 4, 6, 8, 12, 16, 20, and 24; and then every 8 weeks until week 48. A targeted physical examination was performed at baseline, at weeks 4 and 8, and every 8 weeks thereafter. If a subject developed symptoms of MAC infection between scheduled visits, blood specimens were obtained and cultured. When a patient had treatment failure or a relapse, study treatment was discontinued, and the best available salvage therapy was offered through that patient’s primary care provider.

**Mycobacterial blood culture and susceptibility testing.** Peripheral blood was collected in tubes containing sodium polyanetholium sulfate (Vacutainer; Becton Dickinson) and shipped overnight to a central laboratory (Non-Tuberculous Mycobacteria Reference Laboratory, Children’s Hospital, Los Angeles). Blood specimens were cultured for MAC using a radiometric method (Bactec 460TB System; Becton Dickinson Diagnostic Instrument Systems), and bacteremia levels were quantified as described elsewhere [24, 25]. Susceptibility testing for clarithromycin, ethambutol, and rifabutin was performed using radiometric assays in Bactec 12B broth [24–27]. MICs of at least 32, 1, and 16 μg/mL were used to define in vitro resistance to clarithromycin, rifabutin, and ethambutol, respectively.

**Study end points.** The primary study end points were (1) complete microbiologic response by week 12 and (2) complete microbiologic and clinical response by week 12 (defined as achievement of a complete microbiologic response by week 12 and remaining alive and afebrile through week 12). A complete microbiologic response at any given week was defined as 2 consecutive blood cultures negative for MAC without evidence of relapse. A partial microbiologic response was defined as either a single blood culture negative for MAC without evidence of relapse or 2 consecutive cultures showing decreases in the number of MAC colony-forming units, compared with baseline, with at least 1 decrease of ≥1 log_{10} cfu/mL. Treatment failure was defined as the absence of a complete or partial response by a given week or as death, with MAC disease indicated as the primary or contributing cause. Relapse was defined as either a single blood culture positive for MAC with ≥1 log_{10} cfu/mL after a complete or partial response or 2 consecutive increases of at least 1 log_{10} cfu/mL, compared with the week in which a partial response was found. Response was unevaluable in subjects from whom no follow-up samples were obtained for culture through a given week and who did not die as a result of MAC disease; such subjects were considered to have had treatment failure in the intent-to-treat analyses.

Secondary study end points included reduction in the level of MAC bacteremia, the distribution of microbiologic responses (complete, partial, failure, and relapse) at weeks 6–16, relapse, survival, resistance to study drugs, and treatment discontinuation due to drug toxicity.

**Statistical analysis.** This study was designed to test the primary hypothesis that the 3-drug combination would be 25% more effective than each of the 2-drug combinations with regard to the primary end points. The sample size of 195 evaluable patients provided 80% power for each pairwise comparison, using a 2-sided test at a 5% significance level. The overall accrual target was initially increased to 246 subjects to allow for subjects lacking primary end-point data (due to death, loss to follow-up, or missing cultures) but was later reduced to 204 subjects as a result of high end-point evaluability. The NIAID...
Therapeutics Data and Safety Monitoring Board conducted 3 interim analyses of efficacy and safety; O’Brien-Fleming stopping boundaries were used as guidelines for interim monitoring. All P values and 95% CIs presented here are unadjusted for interim analyses.

Fisher’s exact test was used to compare the proportion of patients with complete response in pairwise comparisons and across treatment arms. Pearson’s x² tests (for categorical outcomes) and Kruskal-Wallis tests (for continuous outcomes) were used to compare baseline demographic characteristics. Kaplan-Meier curves and associated log-rank tests were used to compare the distributions of time to complete response, time to relapse, time to death, and time to treatment discontinuation. Cox proportional hazard models were used to evaluate risk factors for survival, and logistic regression models were used to assess predictors of complete microbiologic response. Baseline covariates considered were treatment assignment, CD4+ cell count, previous MAC prophylaxis, PI use, MAC bacteremia level, and resistance of isolates to ethambutol or rifabutin.

RESULTS

Patient Population and Baseline Characteristics

A total of 203 patients were enrolled between December 1994 and February 1998. Thirty-nine subjects had baseline blood cultures that were negative for MAC, and 4 subjects were enrolled but not randomized; these subjects were considered to be ineligible and were excluded from the analysis. Of the 160 eligible subjects, 53 were randomized to receive C+E; 50, C+R;
Figure 2. Change from baseline level of bacteremia, by treatment arm, among patients with AIDS who were receiving treatment for *Mycobacterium avium* complex disease. Bars show 95% CIs. C, clarithromycin; E, ethambutol; R, rifabutin.

and 57, C+E+R. Patients were followed up through June 1998, with a median follow-up period of 41 weeks.

Demographic and selected clinical characteristics and laboratory findings for randomized subjects are summarized in table 1. The median baseline CD4+ T cell count was 8 cells/µL. Previous MAC prophylaxis was reported for 27% of subjects, and 14% were receiving PIs at study entry. The 3 treatment arms were well balanced with regard to baseline characteristics, with no significant differences for any of these measurements.

**Primary Study End Points**

The proportion of subjects with a complete microbiologic response at week 12 was 40% (95% CI, 26%–54%) for the C+E group, 42% (95% CI, 28%–57%) for the C+R group, and 51% (95% CI, 37%–64%) for the C+E+R group (table 2). There were no significant differences between the treatment arms, either overall (P = .454) or in pairwise comparisons. The median time to a complete response was 12–13 weeks for each treatment arm, with no significant difference between treatment arms (P = .964; figure 1). The proportion of patients who developed a complete microbiologic response during follow-up was 55% for C+E, 46% for C+R, and 70% for C+E+R (P = .036). In logistic regression models, only a lower baseline level of MAC bacteremia was significantly associated with a complete response at week 12 (relative risk [RR], 6.06; P<.001).

The proportion of patients who had complete microbiologic and clinical response by week 12 was 26% (95% CI, 15%–40%) for the C+E arm, 26% (95% CI, 15%–40%) for the C+R arm, and 30% (95% CI, 18%–43%) for the C+E+R arm. There were
occurred in the C+R arm, and 16 occurred in the C+E+R arm.

25 deaths occurred in the C+E arm, 25 in the C+E group (7%;

Comparison of the proportions of patients with complete or partial responses who experienced a relapse while receiving C+R (24%) was significant higher than the proportion for the C+E+R group (6%; P = .027) and marginally higher than the proportion for the C+E group (7%; P = .057).

Survival. A total of 66 (41%) of the 160 eligible subjects died during the study; 25 deaths occurred in the C+E arm, 25 occurred in the C+R arm, and 16 occurred in the C+E+R arm.

Progression of HIV-1 infection and MAC disease were the 2 most common causes of death. The median survival times for the C+E group and the C+R group were 35 and 45 weeks, respectively; the median survival time could not be calculated for the C+E+R group, because the estimated survival probability remained >0.50 for the duration of the follow-up period. There was an overall significant difference in time to death (P = .020, by the log-rank test; figure 4), with improved survival for those randomized to receive C+E+R, compared with either C+E (hazard ratio, 0.44; 95% CI, 0.23–0.83; P = .009) or C+R (hazard ratio, 0.49; 95% CI, 0.26–0.92; P = .024). In a multivariate Cox proportional hazards model that was adjusted for PI use and other prognostic factors, treatment with C+E+R was still associated with a significantly decreased risk of death, compared with treatment with C+E (RR, 0.35; P = .002) or C+R (RR, 0.46; P = .026); the association was not statistically significant for any covariate other than treatment.

Resistance of MAC isolates to study drugs. Baseline susceptibility results (available for 156 of the 160 subjects) indicated that only 3 isolates (2%) from samples obtained at baseline were resistant to clarithromycin, whereas 84 (54%) were resistant to ethambutol and 104 (67%) were resistant to rifabutin. The baseline MIC distributions were similar across treatment arms, and there were no significant differences in the proportions of isolates with resistance to clarithromycin, ethambutol, or rifabutin. Most patients (7 of 9) who experienced relapses while receiving C+R had isolates that were resistant to clarithromycin before the relapse, whereas only 1 of 3 patients had resistant isolates in each of the other arms. By the end of follow-up, all but 1 of the 15 patients who had experienced relapses had isolates that were resistant to clarithromycin.

Treatment discontinuation and adverse experiences. There were no significant differences among treatment arms in the time to treatment discontinuation due to toxicity or in the proportion of subjects experiencing such treatment-limiting toxicities (table 4). In addition, there were no differences among treatment arms in the incidence of grade 3 (severe) or 4 (life-threatening) adverse experiences, as defined according to the Division of AIDS Tables for Grading Severity of Adult Adverse Experiences. Gastrointestinal side effects were the most common clinical toxicity, and neutropenia was the most common laboratory toxicity. Confirmed uveitis (any grade) occurred in 8 (5%) of 160 patients. Only 3 cases of uveitis were reported as grade 3 or worse severity, and uveitis resolved in all 8 patients.

DISCUSSION

This study demonstrated no differences in 3 clarithromycin-containing treatment regimens with regard to the primary end point of proportion of patients who achieved a complete mi-
crobiologic response or a complete microbiologic and clinical response by week 12 of therapy. All 3 regimens appeared to provide effective treatment; 70%-84% of patients had either complete or partial microbiologic response by week 12. Planned secondary analyses suggested that the 3-drug regimen, C+E+R, had greater overall efficacy. First, patients randomized to receive C+E+R had a lower risk of death than did patients randomized to receive either of the 2-drug regimens. Second, the rate of relapse was lower in the C+E+R group than in the C+R group. Third, the 3-drug regimen group had the highest proportion of patients who attained a complete response at any point during the study.

Several studies have evaluated the safety and efficacy of clarithromycin in combination with other agents for treatment of MAC disease. Only 2 of these have demonstrated a survival benefit of one regimen compared with another. Shafran et al. [19] evaluated 187 patients with AIDS who had MAC bacteremia and were randomized to receive either rifampin, ethambutol, clofazimine, and ciprofloxacin or clarithromycin, ethambutol, and rifabutin. The clarithromycin regimen was more effective in clearing MAC from blood (clearance in 69% vs. 30% of patients) and showed improved survival (median, 8.7 vs. 5.2 months). The microbiologic response and median survival time were similar to those reported for the C+E+R treatment arm of our study. Chaisson et al. [20] reported contrasting results for 89 patients with AIDS who had MAC bacteremia.
and were randomized to receive either clarithromycin and ethambutol or these drugs plus clofazimine. The clearance of MAC bacteremia, relapse rates, and clinical response were similar between treatment arms, but patients randomized to the 3-drug arm had a higher mortality rate and more treatment-limiting side effects. Our study demonstrated improved survival with the 3-drug regimen of C+E+R, compared with C+E, without greater treatment-limiting toxicity. The clofazimine used in the former study [20] may have contributed to the excess mortality and toxicity observed with the 3-drug regimen.

Finally, Gordin et al. [28] compared the combination of C+E with C+E+R in 198 patients with AIDS who had MAC bacteremia. At week 16, 63% and 61% of patients receiving C+E+R and C+E, respectively, experienced a bacteriologic response to therapy. No differences between treatment arms were reported in clinical improvement or median survival time. No overall differences were noted with regard to development of clarithromycin resistance; however, among patients with bacteriologic responses at week 16, MAC isolates in only 2% of those receiving C+E+R developed clarithromycin resistance, whereas isolates in 14% of those receiving C+E developed resistance. In contrast, the proportions of patients with complete microbiologic response at week 16 in our study were 63% for the C+E+R arm and 47% for the C+E arm. The analysis of the secondary end point of survival in our study indicated that use of C+E+R was associated with improved survival time, com-

![Survival Time (weeks) vs Estimated Survival Probability](https://academic.oup.com/cid/article-abstract/37/9/1234/521802)
in one arm than in another, but rates of treatment discontinuation due to voluntary withdrawal, investigator request, and loss to follow-up were similar across treatment arms.

We conclude that, in our study, the combination of clarithromycin with ethambutol and rifabutin was more effective than a 2-drug regimen of clarithromycin with either ethambutol or rifabutin in prolonging survival, and more effective than clarithromycin plus rifabutin in reducing the risk of relapse. Rifabutin, at the dosage used in this study, did not appear to prevent or delay the emergence of resistance but did appear to contribute to the significant improvement in survival in the 3-drug arm. These data suggest that, with appropriate dose adjustment for drug interactions, the 3-drug combination of clarithromycin, ethambutol, and rifabutin may be among the most effective treatments for disseminated MAC disease in HIV-infected individuals.

### Participating Sites in the AIDS Clinical Trials Group Protocol 233

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of Cincinnati, Cincinnati, Ohio (Richard Greenberg); Indiana University Hospital, Indianapolis (Kristen Todd, Beth Zwick, Sarah Ryan, and John Black); Cook County Hospital, Chicago, Illinois (Joseph Pulvirenti); University of North Carolina, Chapel Hill (Charles van der Horst, Irene Vangness, and Barbara Longmire); University of Hawaii, Honolulu (Monica Millard); University of Alabama at Birmingham (Donna Davis and Bob Hill); Emory University, Atlanta, Georgia (Robert Horsburgh and Molly Eaton); University of Colorado Health Sciences Center, Denver (Graham Ray, Steven Johnson, and Michael Grodesky); and Vanderbilt University, Nashville, Tennessee (Judy McKinsey).

References


