Clarithromycin or Rifabutin Alone or in Combination for Primary Prophylaxis of *Mycobacterium avium* Complex Disease in Patients with AIDS: A Randomized, Double-Blind, Placebo-Controlled Trial

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The efficacy and safety of clarithromycin and rifabutin alone and in combination for prevention of *Mycobacterium avium* complex (MAC) disease were compared in 1178 patients with AIDS who had ≤100 CD4 T cells/μL in a randomized, double-blind, placebo-controlled trial. MAC disease occurred in 9%, 15%, and 7% of those randomized to clarithromycin or rifabutin alone or in combination, respectively; time-adjusted event rates per 100 patient-years (95% confidence interval [CI]) were 6.3 (4.2–8.3), 10.5 (7.8–13.2), and 4.7 (2.9–6.5). Risk of MAC disease was reduced by 44% with clarithromycin (risk ratio [RR], 0.56; 95% CI, 0.37–0.84; $P = .005$) and by 57% with combination therapy (RR, 0.43; 95% CI, 0.27–0.69; $P = .0003$), versus rifabutin. Combination therapy was not more effective than clarithromycin (RR, 0.79; 95% CI, 0.48–1.31; $P = .36$). Of those in whom clarithromycin or combination therapy failed, 29% and 27% of MAC isolates, respectively, were resistant to clarithromycin. There were no survival differences. Clarithromycin and combination therapy were more effective than rifabutin for prevention of MAC disease, but combination therapy was associated with more adverse effects (31%; $P < .001$).

Although the incidence of *Mycobacterium avium* complex (MAC) disease has declined dramatically with the widespread use of potent antiretroviral therapy, the risk of developing disseminated MAC disease for persons with human immunodeficiency virus (HIV) infection remains substantial for those with <50 CD4 T cells/μL, a prior opportunistic infection, or high plasma HIV RNA levels [1–8]. In the absence of prophylaxis and potent antiretroviral therapy, the incidence of MAC disease

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The protocol was reviewed and approved by the institutional review boards of all participating institutions. Informed consent was obtained from all subjects, and human experimentation guidelines of the US Department of Health and Human Services and the local institutional review boards at all participating sites were followed. The study was monitored by the National Institute of Allergy and Infectious Diseases (NIAID) Data and Safety Monitoring Board.

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ranges from 12% to 24% [2, 3, 5]. Because specific interventions that reduce exposure to environmental MAC have not been established, control of HIV-1 replication and chemoprophylaxis are the principal approaches to prevention [2–4, 8–16].

Chemoprophylaxis for MAC disease is recommended for all HIV-infected persons with <50 CD4 T cells/μL [16]. Rifabutin reduces the incidence of MAC bacteremia by 55% and improves survival, when compared with patients at risk who are not receiving rifabutin [17, 18]. Clarithromycin reduces the incidence of MAC bacteremia by 69% and improves survival by 30%, when compared with placebo recipients [19]. Azithromycin reduces the incidence of MAC bacteremia by 57%, compared with placebo; a survival benefit has not been demonstrated [20]. Azithromycin is more effective than rifabutin in reducing the incidence of MAC disease, and the combination of azithromycin plus rifabutin is more effective than either drug alone [21]. The present study was undertaken to compare the safety and efficacy of clarithromycin with rifabutin and with the combination of clarithromycin and rifabutin in preventing disseminated MAC disease and the emergence of resistant isolates during chemoprophylaxis.

Methods

Study design. This study was a prospective, multicenter, randomized, double-blinded, placebo-controlled trial of clarithromycin (provided by Abbott Laboratories, Abbott Park, IL), rifabutin (provided by Adria Laboratories, Dublin, OH, and Pharmacia & Upjohn, Kalamazoo, MI), or the combination of clarithromycin and rifabutin for the prevention of MAC disease in HIV-infected persons with ≤100 CD4 T lymphocytes/μL. The study was conducted at 37 adult and pediatric sites of the National Institute of Allergy and Infectious Diseases (NIAID) AIDS Clinical Trials Group (ACTG) and 13 sites of the NIAID Terry Beirn Community Programs for Clinical Research on AIDS (CPCRA). Subjects were recruited from referral and primary care patient populations at each site.

Patients were eligible if they were ≥12 years of age, had laboratory evidence of HIV infection, ≤100 CD4 T lymphocytes/μL within 90 days of study entry, 2 blood cultures negative for MAC ≥1 week apart within 30 days of study entry, no signs or symptoms of MAC disease, and a Karnofsky performance score ≥50. Laboratory eligibility requirements included no evidence of active pulmonary disease on a chest radiograph, ≥8 g/dL hemoglobin, absolute neutrophil count of ≥500 cells/μL, platelet count of ≥50,000 cells/μL, and serum aspartate aminotransferase, bilirubin, and serum creatinine levels ≤5 times, <2.5 times, and <2 times the upper limit of normal, respectively. Antiretroviral therapy and prophylaxis for *Pneumocystis carinii* pneumonia were encouraged for all patients. Subjects were excluded if they had known or suspected MAC disease, other mycobacterial infection requiring treatment (with the exception of latent tuberculosis for which isoniazid chemoprophylaxis was allowed), hypersensitivity to study medications, concurrent use of terfenadine or astemizole, pregnancy or lactation, a history of ≥4 months of therapy with clarithromycin, azithromycin, or rifabutin in the year prior to study entry, or malabsorption as defined by persistent diarrhea of >6 stools per day for >6 weeks.

After eligibility was confirmed, subjects were randomized—in equal proportions by use of permuted blocks of 6—to receive either clarithromycin 500 mg 2 times a day, rifabutin 450 mg once per day, or combination therapy in the same doses. Randomization was done centrally by the Statistical and Data Management Center of the Adult ACTG (without direction from the pharmaceutical sponsors). Sites, patients, and participating clinicians remained blinded to treatment assignment and dose; only study statisticians had access to treatment codes. The rifabutin dose of 450 mg once per day was selected to determine whether this dose could improve the efficacy observed with the dose of 300 mg once per day used in earlier placebo-controlled trials [17]. The study design specified that 1100 patients be accrued over a 1-year period and followed for 18 months after the last patient enrolled. The recognition of an increased risk of uveitis in persons receiving clarithromycin and rifabutin prompted a modification of the study design 9 months after implementation (March 1994), to reduce the dose of rifabutin to 300 mg once per day [22–24].

Patients were evaluated for signs and symptoms of MAC disease, adverse events, adherence, and temperature, weight, and Karnofsky performance score at weeks 4 and 8 and every 8 weeks thereafter. A targeted physical examination, including vital signs and examination of lymph nodes, liver, and spleen, was done at baseline, at weeks 24, 48, 72, and 96, and at interim visits if symptoms warranted. Blood for MAC culture was obtained for all enrolled participants, including those who prematurely discontinued study medications, at baseline and every 8 weeks thereafter. At each study visit, blood was obtained for hemoglobin, total white blood cell, absolute neutrophil, and platelet counts, as well as levels of aspartate aminotransferase, total bilirubin, alkaline phosphatase, serum creatinine, and albumin. Specimens of blood or other sterile sites were obtained for MAC culture at interim visits if patients developed signs or symptoms of MAC disease as defined by one or more of the following: fever >38.3°C for ≥7 days, night sweats, hepatomegaly, splenomegaly, elevated serum alkaline phosphatase level (>2.5 times the upper limit of normal), development of new or worsening anemia, diarrhea of >6 stools per day for ≥7 days, or weight loss of >10% of body weight. CD4 T cell counts were repeated at weeks 48 and 96.

A dose reduction of clarithromycin to 500 mg per day was allowed for patients with recurrent adverse effects of grade 3 or higher severity or for unremitting gastrointestinal adverse effects of grade 2 severity, as defined according to NIAID Division of AIDS tables for grading severity of adult adverse experiences. Patients who prematurely discontinued study medications were followed for survival and development of MAC disease.

Mycobacterial blood culture and susceptibility tests. Peripheral blood was collected in tubes containing sodium polyanetholium sulfate (Becton Dickinson Vacutainer Systems, Rutherford, NJ) and shipped overnight at ambient temperature to a central laboratory (National Jewish Medical Research Center, Denver). Blood specimens were processed for MAC culture and organisms isolated in 7H12 broth by a radiometric method (BACTEC 12B; Becton Dickinson Diagnostic Instrument Systems, Sparks, MD) and on 7H11 agar for quantitation as described elsewhere [25]. *Mycobacterium* species were identified by use of hybridization probes for

M. avium, M. intracellulare, MAC, *M. tuberculosis,* and *M. kansasii* (AccuProbe; Gen-Probe, San Diego). In some instances, cultures for MAC were obtained from sterile sites other than blood or from blood at interim visits; these were processed locally and, when feasible, were shipped to the central laboratory for susceptibility testing. Susceptibility testing to clarithromycin and rifabutin was performed radiometrically in 7H12 broth by methods described elsewhere; a MIC >32 μg/mL was used to indicate clarithromycin resistance [26–28].

Study end points. The primary study end point was the development of MAC disease as defined by a single blood culture positive for MAC after randomization or the isolation of MAC from another normally sterile site plus at least 1 sign or symptom of MAC disease, as previously defined. Secondary end points included death, treatment-limiting adverse effects, and susceptibility of MAC isolates to study medications. Death was attributed to MAC disease if cultures of blood or other normally sterile sites were positive for MAC and, in the opinion of the participating site investigator, no other cause of death was determined.

Statistical analysis. The Statistical and Data Analysis Center of the ACTG analyzed all data. The study was designed to test 2 primary hypotheses: the null hypothesis that there was no difference in the rates of development of MAC disease for the combination of clarithromycin with rifabutin compared with either of the 2 single agents and that the 2 single agents were equivalent with respect to their rates of development of MAC disease. Each analysis was conducted at an overall significance level of $\leq$.05, and individual comparisons with each single agent were tested at the .025 significance level to ensure an overall .05 level for the first primary hypothesis. Two interim analyses of efficacy and safety were conducted by the NIAID Data and Safety Monitoring Board in August 1994 and February 1995. Stopping guidelines for interim monitoring were based on the O'Brien-Fleming boundaries corresponding to a Lan-DeMets use function.

It was assumed that the yearly rate of development of MAC disease in the rifabutin and clarithromycin treatment arms would be 11.67% per year and that combination therapy would reduce the rate by 50% with either of the 2 single agents [17]. The sample size of 1100 provided at least 80% power for testing the equivalence hypothesis for the 2 single-drug arms at a significance level of $\leq$.05 and provided 90% power for testing the null hypothesis of no difference between either rifabutin or clarithromycin and the combination of rifabutin or clarithromycin, both at a significance level of $\leq$.025.

Standard pairwise log-rank tests were used to compare treatment regimens with respect to distributions of time to events. Two-sided 95% confidence intervals (CIs) on the hazard ratio were constructed to compare the equivalence of the 2 single agents. A Cox proportional hazards model was used in a multivariate analysis to evaluate risk factors for development of MAC disease. Other analyses of treatment differences relied on comparisons of the proportions of patients within subsets and used Pearson's χ^2 tests of association or Cochran-Mantel-Haenszel χ^2 tests of trend for categories that had natural ordering. For analyses of risk factors that had only 2 categories, Fisher's exact test was used to compare proportions among treatment groups.

An intent-to-treat approach was used in evaluating all primary and secondary objectives. As secondary supportive evaluations, "as-treated" analyses were conducted that compared treatment regimens with respect to time to MAC disease and to death; these analyses included only those events that occurred while patients were receiving assigned treatment or within 30 days of treatment discontinuation.

Results

Patient population. In total, 1216 patients were enrolled between April 1993 and February 1994. Five patients were inadvertently enrolled, and 33 were determined to have positive MAC blood cultures at entry and were excluded. Of the 1178 eligible subjects, 398 were randomized to clarithromycin, 391 to rifabutin, and 389 to combination therapy. Exemptions for minor protocol-defined eligibility criteria were granted for 43 patients. Patients were followed through August 1995, with a median duration of follow-up of 595, 574, and 595 days for the clarithromycin, rifabutin, and combination arms, respectively.

Demographic and selected clinical characteristics of randomized subjects are summarized in table 1. The median age was 38 years, the median CD4 T cell count was 28 cells/μL, and the median Karnofsky performance score was 90. Overall, 97% were receiving *P. carinii* pneumonia prophylaxis; 74% were currently or had been previously treated with antiretroviral therapy; however, of those enrolled at ACTG sites, 83% were antiretroviral experienced, compared with only 49% of those enrolled at CPCRA sites ($P < .001$). The antiretroviral therapies consisted primarily of mono- or dual-combination therapy with nucleoside reverse-transcriptase inhibitors. The types of antiretroviral therapies did not differ among treatment groups. Other baseline characteristics were similar across all 3 treatment groups and both clinical trials groups.

MAC disease end points. For the primary intent-to-treat analysis, 121 subjects developed confirmed MAC end points; 36 (9%) of those randomized to clarithromycin, 59 (15%) to rifabutin, and 26 (7%) to combination therapy. The time-adjusted event rates per 100 patient-years (95% CI) were 6.3 (4.2–8.3) for the clarithromycin treatment arm, 10.5 (7.8–13.2) for the rifabutin arm, and 4.7 (2.9–6.5) for the combination arm. Pairwise comparisons based on a Kaplan-Meier analysis of time to MAC disease by treatment (figure 1) indicated that patients randomized to rifabutin were more likely to develop MAC disease than those who received clarithromycin (P = .005) or combination therapy (P = .0003; table 2). Clarithromycin reduced the risk of MAC disease by 44% (risk ratio [RR], 0.56; 95% CI, 0.37–0.84; P = .005), and combination therapy reduced the risk by 57% (RR, 0.43; 95% CI, 0.27–0.69; P = .0003), compared with rifabutin. There was no significant difference in the time to development of MAC disease for clarithromycin versus combination therapy (RR, 0.79; 95% CI, 0.48–1.31; P = .36). Of 121 patients, 78 (64%) were receiving assigned study drug at the time they developed a MAC end

Table 1. Selected baseline characteristics of study participants by treatment arm.

Characteristic	Total (n = 1178)	Clarithromycin (n = 398)	Rifabutin (n = 391)	Combination therapy (n = 389)
Sex				
Men	1061 (90)	356 (89)	353 (90)	352 (90)
Women	117 (10)	42 (11)	38 (10)	37 (10)
Race/ethnicity				
White	731 (62)	250 (63)	243 (62)	238 (61)
African American	300 (25)	94 (24)	110 (28)	96 (25)
Latino	127 (11)	45 (11)	32 (8)	50 (13)
Other	20 (2)	9 (2)	6 (2)	5 (2)
Injection drug use, current/previous	181 (15)	64 (16)	61 (16)	56 (15)
Median age (years)	38	37	39	39
Median CD4 cells/μL	28	27	30	28
Median Karnofsky score	90	90	90	90
Antiretroviral experience				
Never or unknown	310 (26)	107 (27)	97 (25)	106 (27)
Current/previous use	868 (74)	291 (73)	294 (75)	283 (73)

NOTE. Data are no. (%) except where noted otherwise.

point; an additional 5 end points occurred within 30 days of treatment discontinuation. The results of the as-treated analysis were similar to those of the intent-to-treat analysis (table 2). For both analyses, the 2-year event rates were more than twice the 1-year event rates for the combination arm and 3 times the 1-year event rates for each of the single agents.

In a multivariate Cox proportional hazards model, patients with baseline CD4 T lymphocyte counts <50 cells/μL had 2.9 times (95% CI, 1.8–4.7) the risk of developing MAC disease than those with ⩾50 CD4 cells/μL. Patients with a baseline Karnofsky score ⩽80 had 1.8 times (95% CI, 1.3–2.6) the risk of developing MAC disease than those with Karnofsky scores >80. Analyses of time to development of MAC disease according to rifabutin dose reduction as a time-dependent covariate showed that those receiving the reduced dose of rifabutin (300 mg once per day) were less likely to develop MAC disease (RR, 0.34; 95% CI, 0.23–0.50; P = .0001) than those who did not stay on study drug or on assigned treatment long enough to reach the study-wide rifabutin dose reduction. In this multivariate model, treatment comparisons with rifabutin remained significant even after adjustment for baseline CD4 T cell count and Karnofsky score. Of the 1178 patients, 402 had already discontinued treatment or reduced their rifabutin dosage by the time of the study-wide decrease in rifabutin dose. No significant association with risk of MAC disease was identified for other potential risk factors, including gender, hemoglobin at entry, parenteral drug use, and use of antiretroviral agents prior to entry.

Identification, quantitation, and drug susceptibility testing of MAC isolates. All but 3 breakthrough isolates were identified as MAC; the rest were identified as *M. intracellulare.* The organism burden was low for the majority of patients in whom prophylaxis failed; for 80%, the number of viable bacteria was 1–8 cfu/mL of blood, and only 7% had >100 cfu/mL of blood. There were no significant differences in quantitative mycobacteremia among the treatment groups.

Isolates were available for susceptibility testing for 90 of the 121 patients who developed MAC end points (table 3). Thirty-one isolates (randomly distributed across treatment arms) were recovered and identified at local laboratories and were not referred to the central laboratory for susceptibility testing, because either they failed to grow on subculture or the isolates were not made available by the local laboratory. These isolates were included in the determination of primary end points if hard copy laboratory reports were available for confirmation; they were not included in susceptibility-testing analyses. The proportion of tested isolates with MICs >32 μg/mL for clarithromycin was 7 (29%) of 24 in the clarithromycin arm and 4 (27%) of 15 in the combination arm; no isolates from patients randomized to rifabutin had clarithromycin MICs >2 μg/mL. There was a significant trend toward higher clarithromycin MICs in the clarithromycin arm versus the rifabutin arm (trend test, $P \leqslant .001$) and for the combination arm versus the rifabutin arm (trend test, $P \leqslant .001$); however, there was no difference for clarithromycin alone versus combination therapy (trend test, P = .784). Overall, <2% of patients randomized to a clarithromycin arm developed MAC disease with an isolate resistant to clarithromycin. There were no differences in susceptibility to rifabutin (Pearson's χ^2 test, P = .307) and no trend toward higher rifabutin MICs among the 3 arms (trend test, P = .948).

Survival. A total of 514 patients died during the study: 167 randomized to clarithromycin, 168 to rifabutin, and 179 to combination therapy. The rates (95% CI) per 100 person-years were 29.1 (24.7–33.5), 29.8 (25.3–34.4), and 32.2 (27.5–36.9), respectively. Pairwise comparisons indicated no differences between clarithromycin and rifabutin (RR, 0.97; 95% CI, 0.78–1.20; P = .79), between clarithromycin and combination therapy (RR, 0.89; 95% CI, 0.72–1.10; P = .28), or between rifabutin and combination therapy (RR, 0.92; 95% CI, 0.74–1.13; P = .42). A Kaplan-Meier analysis of survival distributions for time to death by treatment showed no difference among treatment arms (log-rank test, P = .533). In the as-treated analysis, there were 239 deaths with no differences among treatment

arms (log-rank test, $P = .519$). The primary cause of death was attributed to MAC disease for only 4% of those who died.

Adverse experiences. Among the 1178 eligible participants, gastrointestinal side effects were the most frequently reported treatment-related serious adverse effects. For the clarithromycin, rifabutin, and combination arms, the percentage of patients with nausea or vomiting of grade 3 (severe discomfort or minimal intake for ⩾3 days) or higher severity was 2.5%, 3.6%, and 4.6%, respectively. Similarly, 4.3%, 6.7%, and 4.6%, respectively, reported diarrhea of grade 3 (bloody diarrhea, orthostatic hypotension, >7 loose stools per day, or parenteral hydration required) or higher severity (table 3). With the exception of abdominal pain, which was more frequent among those on the 2 single-agent arms compared with the combination arm, there were no differences among the treatment arms with respect to gastrointestinal signs or symptoms, serum or liver chemistry, or hematologic laboratory abnormalities (table 3). Neutropenia was the most common hematologic adverse effect, with 24.8% of patients experiencing a grade 3 (500–749/μL) or worse absolute neutrophil count; however, only 1.1% of patients had treatment discontinued due to neutropenia. The time to first grade 3 or worse liver chemistry or hematologic adverse events did not differ by treatment arm. However, the overall time to first grade 3 or worse gastrointestinal toxicity was significantly different ($P = .039$); subjects receiving clarithromycin had significantly lower risk of gastrointestinal toxicities than those on rifabutin ($P = .011$) and a marginally lower risk than those on combination therapy ($P = .077$).

Seventy patients had a protocol-defined treatment-limiting toxicity; an additional 184 patients voluntarily discontinued study medication because of a toxicity severity less than grade 3. Gastrointestinal intolerance was the primary reason for a protocol-defined or voluntary treatment discontinuation. A Kaplan-Meier analysis of the time to permanent treatment discontinuation due to toxicity indicated that subjects randomized to combination therapy were more likely to discontinue treatment than those randomized to clarithromycin (RR, 2.28; 95% CI, 1.68–3.09; $P < .0001$) or rifabutin (RR, 1.91; 95% CI, 1.42–2.56; $P < .0001$); there was no difference between clarithromycin and rifabutin (RR, 0.83; 95% CI, 0.59–1.17; $P = .29$).

Uveitis developed in 42 patients (3.6%). Overall, the adjusted uveitis event rate was 2.6 per 100 patient-years of follow-up. Of the 42 subjects with uveitis, 33 (78.6%) were receiving combination therapy, 7 (16.7%) rifabutin, and 2 (4.7%) clarithromycin. Uveitis developed a median of 18 weeks after the time of randomization. The uveitis rate before the study-wide dose reduction of rifabutin from 450 to 300 mg was 5.68 events per 100 patient-years; after the dose reduction, it was 1.40 per 100

Table 2. Pairwise comparisons with risk ratios for time to *Mycobacterium avium* complex disease, by treatment arm.

Treatment comparison	Risk ratio (95% confidence interval)	Log-rank *P*
Intent to treat		
Clarithromycin vs. rifabutin	0.56 (0.37–0.84)	.005
Combination vs. clarithromycin	0.79 (0.48–1.31)	.360
Combination vs. rifabutin	0.43 (0.27–0.69)	<.001
As treated		
Clarithromycin vs. rifabutin	0.46 (0.27–0.76)	.002
Combination vs. clarithromycin	0.89 (0.47–1.68)	.714
Combination vs. rifabutin	0.41 (0.23–0.74)	.002

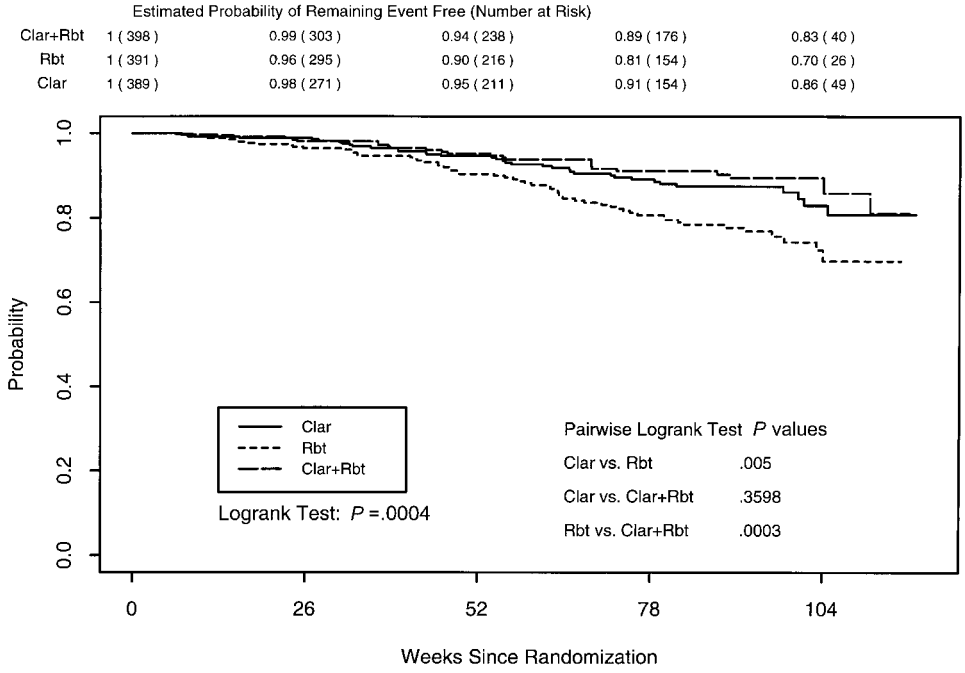

Figure 1. Kaplan-Meier plot of time to confirmed *Mycobacterium avium* complex disease, by treatment arm. Clar, clarithromycin; Rbt, rifabutin.

Table 3. Proportion (%) of patients with treatment-limiting toxicities or adverse effects of grade 3 or higher severity, by treatment arm.

Symptom/Sign	Clarithromycin (n = 398)	Rifabutin (n = 391)	Combination therapy (n = 389)
Treatment-limiting toxicity	15.8	18.2	30.8[a]
Protocol defined	3.5	5.6	8.7
Voluntary discontinuation	12.3	12.5	22.1
Gastrointestinal adverse effects of grade 3 or higher severity			
Abdominal pain	5.0	4.6	2.1
Nausea/vomiting	2.5	3.6	4.6
Diarrhea	4.3	6.7	4.6
Laboratory adverse effects of grade 3 or higher severity			
Hemoglobin	3.0	2.3	2.3
Absolute neutrophil count	24.1	24.6	25.7
Platelets	5.5	4.6	5.4
Alkaline phosphatase	3.5	2.6	3.6
Aspartate aminotransferase	8.5	6.4	8.0
Total bilirubin	2.5	2.3	3.9
Creatinine	1.0	1.0	0.5
Uveitis	0.5	1.8	8.5[b]

[a] $P < .001$ (log-rank test comparing 3 treatment arms with respect to time to event); includes both voluntary and protocol-mandated discontinuation of study medication because of adverse effect; $P = .017$ (Pearson's χ^2 test).

[b] $P < .0001$ (log-rank test comparing 3 treatment arms with respect to time to event).

patient-years, similar to the rate of 1.03 events per 100 patient-years observed after patients had permanently discontinued all study treatment. Uveitis resolved in all subjects after discontinuation of study medications and/or use of supportive therapy.

Discussion

This study demonstrated that both clarithromycin and the combination of clarithromycin with rifabutin were more effective in reducing the occurrence of MAC disease than was rifabutin alone in HIV-infected persons with ≤100 CD4 cells/μL. Clarithromycin reduced the incidence of MAC disease by 44% and combination therapy by 57%, compared with rifabutin. Of the isolates tested from subjects in whom clarithromycin therapy failed, 29% were clarithromycin resistant. The addition of rifabutin to clarithromycin did not substantively reduce the development of clarithromycin resistance. Chemoprophylaxis with either clarithromycin or rifabutin was generally well tolerated, with few treatment-limiting adverse effects, although combination therapy was associated with a higher rate of intolerance. One unique adverse effect, seen predominantly in the combination treatment arm, was uveitis. Uveitis has been attributed to high levels of rifabutin, in this instance presumably as a consequence of its combination with clarithromycin [22]. Once the dose of rifabutin was reduced to 300 mg daily, the rate of uveitis was substantially reduced. Paradoxically, subjects who received the reduced dose of rifabutin were seemingly at lower risk of developing MAC disease than those originally randomized to the higher dose. This may be attributable to the fact that those who remained on treatment long enough to reach the study-wide dose reduction were healthier and less likely to develop a treatment-limiting toxicity.

The efficacy data in our study are similar to results described by Pierce et al. [19], who showed that clarithromycin reduced the incidence of MAC bacteremia by 69% compared with placebo. In contrast to the latter study, which also showed clarithromycin reduced mortality by 30%, we did not demonstrate differences in survival between the treatment arms. There are a number of possible explanations for this difference. Our study did not compare treatment to a placebo. The longer duration of follow-up in our study (19.5 vs. 10 months in the study by Pierce et al.) may have placed patients at increased risk for death due to competing causes. The availability of improved treatments for MAC and HIV disease may have contributed to improved survival in all treatment arms. Each of these factors may thus have diminished the power to detect individual survival differences related to reductions in MAC disease in our study.

Resistance of breakthrough isolates to clarithromycin was observed in both our study and the placebo-controlled trial of clarithromycin [19]. Pierce et al. [19] reported that, of 19 MAC isolates recovered from patients in whom clarithromycin failed, 58% were resistant to clarithromycin, which is a substantially higher rate than in our study. However, the overall incidence of disease due to clarithromycin-resistant MAC was <2% for both studies [19]. The higher resistance seen in the study by Pierce et al. remains unexplained.

In another study, similar in design to ours, Havlir et al. [21] randomized 693 HIV-infected persons to receive azithromycin 1200 mg once per week, rifabutin 300 mg once per day, or combination therapy for prophylaxis of MAC disease. In the intent-to-treat analysis, the incidence of MAC disease in the azithromycin arms was similar to that in the clarithromycin arms of our study, whereas only 15% of those randomized to rifabutin in our study developed MAC disease despite a slightly longer duration of drug exposure, compared with 23.3% in the study by Havlir et al. Pairwise comparisons of the incidence of MAC disease were also similar for the single and combination arms in both studies, although the magnitude of reduction in relative risk, compared with that for rifabutin, was greater for the azithromycin-rifabutin combination (72%) than for the clarithromycin-rifabutin combination (57%) in our study. Of MAC isolates from patients receiving azithromycin in the former study, 18% were resistant to azithromycin and clarithromycin versus 29% randomized to clarithromycin in our study; none obtained from those randomized to the combination arm were resistant compared with 27% in our study. As with our results, there were no survival differences among the 3 arms.

A number of hypotheses may explain the differences in efficacy and resistance between these 2 studies. First, clarithromycin has lower MICs in vitro for MAC isolates than azithromycin and, when coupled with daily doses in our study, may

have provided greater activity than a once weekly dose of azithromycin, such that the addition of rifabutin did not further increase the efficacy of clarithromycin. Second, the bidirectional interaction between clarithromycin and rifabutin may have reduced plasma concentrations of clarithromycin, thus interfering with the activity of combination therapy [22]. Although there is an attendant increase in rifabutin plasma concentrations due to this interaction, this may not have been sufficient to result in an additive or synergistic effect of combination therapy. Third, a larger proportion of subjects receiving combination therapy in our study discontinued study treatment due to toxicity and did so at an earlier time point than in the study by Havlir et al. [21], reducing overall treatment exposure and possibly the ability to detect differences in efficacy or resistance in our study. Fourth, subjects were followed for a modestly longer duration in our study and had blood cultures monitored every 2 months rather than monthly as in the study by Havlir et al. This might have afforded a longer duration of exposure to clarithromycin monotherapy for individuals before MAC bacteremia was detected. Relapse with a clarithromycin-resistant isolate of MAC has been seen as early as 8 weeks after onset of treatment with clarithromycin monotherapy in patients with AIDS and MAC bacteremia [29]. Finally, in the study by Havlir et al., the percentage of patients randomized to rifabutin who developed MAC disease was greater than that in our study, perhaps contributing to the greater differences between azithromycin or combination therapy when compared with rifabutin in that study.

One limitation of our study is that it was conducted during the era of mono- and dual nucleoside antiretroviral therapy. More potent antiretroviral therapy has reduced the incidence of opportunistic infections, including MAC disease, in persons who have increases in CD4 T lymphocyte counts and reductions in plasma HIV-1 RNA levels [1]. Although clinical trials are ongoing, observational data suggest that primary prophylaxis for some opportunistic infections may be safely discontinued in subjects who sustain these immunologic and virologic responses [30, 31]. However, chemoprophylaxis is still recommended for those who have <50 CD4 T cells/μL, regardless of antiretroviral therapy [32]. In addition, the present study was also not able to address other key issues related to MAC prophylaxis, such as the comparative efficacy of clarithromycin and azithromycin, other dosing schedules of clarithromycin, the impact of prophylaxis with clarithromycin on the ability to treat MAC disease, particularly for those who develop disease due to a drug-resistant isolate, and macrolide resistance in those who develop bacterial infections. These remain important clinical concerns for those who require prophylaxis.

This study supports the recommendation for use of clarithromycin as a first-line agent for the prevention of MAC disease in persons with HIV infection and advanced immunosuppression but not the use of combination therapy for prophylaxis. Drug interactions associated with clarithromycin inhibition of the 3A4 isoenzyme of the cytochrome P450 system may complicate its use with other drugs metabolized by this pathway (e.g., protease inhibitors or nonnucleoside reverse-transcriptase inhibitors). As a consequence, when chemoprophylaxis for MAC disease is indicated, decisions regarding use of clarithromycin should be individualized.

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