Once Weekly Azithromycin Therapy for Prevention of \textit{Mycobacterium avium} Complex Infection in Patients with AIDS: A Randomized, Double-Blind, Placebo-Controlled Multicenter Trial


We conducted a randomized, double-blind, placebo-controlled multicenter trial of azithromycin (1,200 mg once weekly) for the prevention of \textit{Mycobacterium avium} complex (MAC) infection in patients with AIDS and a CD4 cell count of <100/mm$^3$. In an intent-to-treat analysis through the end of therapy plus 30 days, nine (10.6\%) of 85 azithromycin recipients and 22 (24.7\%) of 89 placebo recipients developed MAC infection (hazard ratio, 0.34; $P=0.004$). There was no difference in the ranges of minimal inhibitory concentrations of either clarithromycin or azithromycin for the five breakthrough (first) MAC isolates from the azithromycin group and the 18 breakthrough MAC isolates from the placebo group. Of the 76 patients who died during the study, four (10.5\%) of 38 azithromycin recipients and 12 (31.6\%) of 38 placebo recipients had a MAC infection followed by death ($P=0.025$). For deaths due to all causes, there was no difference in time to death or number of deaths between the two groups. Episodes of non-MAC bacterial infection per 100 patient years occurred in 43 azithromycin recipients and 88 placebo recipients (relative risk, 0.49; 95\% confidence interval, 0.33–0.73). The most common toxic effect noted during the study was gastrointestinal, reported by 78.9\% of azithromycin recipients and 27.5\% of placebo recipients. Azithromycin given once weekly is safe and effective in preventing disseminated MAC infection, death due to MAC infection, and respiratory tract infections in patients with AIDS and CD4 cell counts of <100/mm$^3$.

\textit{Mycobacterium avium} complex (MAC) infection is the most common cause of bacterial opportunistic infections in persons with AIDS in the United States [1]. After a diagnosis of AIDS, the incidence of MAC bacteremia was found to be 21\% at 1 year and 43\% at 2 years when monthly lysis centrifugation blood cultures were routinely performed [2]. Among those patients with a CD4 cell count of <50/mm$^3$, the incidence is even higher: 32\% at 6 months and 51\% at 1 year [3]. As the survival of patients with AIDS has increased with improved antiretroviral regimens and prophylaxis for pneumocystis infection, the incidence of MAC infection has progressively increased.

The survival of patients with MAC infection is shorter (107–139 days) than that of patients with AIDS but without MAC infection (275–330 days) [4–6]. As would be expected from the increasing incidence of MAC infection, the rate of deaths due to MAC infection in patients with AIDS has also increased from 6.7\% in 1987 to 12.2\% in 1992 [7].

With the availability of the macrolides and effective combination therapy, survival after a diagnosis of MAC infection has increased from 4.5 months without treatment to ~9 months [3, 4, 8]. However, the need for effective prophylaxis is suggested by the fact that as many as 23\% of patients may die before or within 4 weeks of the initial positive culture result for MAC [3].

On the basis of reports of two large prospective trials that revealed an ~50\% reduction in the incidence of MAC infection, the Public Health Service Task Force on Prophylaxis and Therapy for \textit{Mycobacterium avium} Complex recommended prophylaxis with rifabutin (300 mg/d) for patients with AIDS and a CD4 T lymphocyte count of <100/mm$^3$ [9, 10]. Although
rifabutin has been a significant advance in prophylaxis for MAC infection, its efficacy is only modest, and there are a number of drawbacks, including the numerous potential drug interactions, high cost, problems with compliance associated with daily therapy, and the potential of Mycobacterium tuberculosis to produce cross-resistance to rifampin.

Azithromycin is an azalide differing from erythromycin only at the 9 position of the macrolide ring. Serum levels are low (0.4 µg/mL after a 500-mg dose [11]), and activity against MAC in vitro has been modest. In a study of 15 MAC strains, the MIC<sub>90</sub> was 64 µg/mL, while all bactericidal values were >64 µg/mL [12]. However, azithromycin achieves tissue levels that are 10-200-fold higher than serum levels with a prolonged half-life of 3 days. The concentration in macrophages, the site of replication of MAC, is >500-fold higher than serum levels [13]. Azithromycin monotherapy (500 mg/d) for patients with AIDS and MAC bacteremia resulted in a 1.3 log reduction in MAC cfu/mL in blood cultures and resolution of fever and sweats in two-thirds of patients [14].

Because of the favorable pharmacokinetics, which allow once weekly dosing, and encouraging results of therapy for MAC infection in humans, we undertook a study of azithromycin for prevention of MAC infection in patients with AIDS and a CD4 lymphocyte count of <100/mm<sup>3</sup>. This placebo-controlled trial is a companion study to the comparative trial of azithromycin vs. rifabutin vs. azithromycin plus rifabutin [15].

**Methods**

**Study Design**

We conducted a randomized, double-blind, placebo-controlled multicenter trial of once weekly azithromycin for the prevention of MAC infection in patients with AIDS. Men and nonpregnant women who were HIV-seropositive and 18 years of age or older were eligible for the study. Subjects had to have had one documented CD4 cell count of <100/mm<sup>3</sup> within the preceding 12 months. Two blood specimens for MAC cultures were obtained, one at the screening visit and one at 3–5 weeks after the baseline visit.

Criteria for exclusion included a positive blood culture for MAC at screening or baseline, symptoms suggestive of MAC infection (including unexplained diarrhea, fever, or night sweats), a history of MAC infection, or known or suspected M. tuberculosis infection. Subjects treated in the 4 weeks before enrollment with any putative therapy for MAC infection or who had a known hypersensitivity to macrolides also were excluded. Subjects for whom screening laboratory tests revealed values for aminotransferases and alkaline phosphatase that were greater than five times the upper limit of normal, a total bilirubin level of >2.5 mg/dL, a creatinine level of >2.5 mg/dL, or a neutrophil count of <0.50 × 10<sup>9</sup>/L were excluded.

The protocol was approved by the Institutional Review Board at each of the participating centers. Informed consent was obtained from each study subject before enrollment.

Patients were randomly assigned in a one-to-one ratio by a computer-generated random code in blocks of four to receive either azithromycin or placebo. Azithromycin was given as four 300-mg lactose-free tablets in a single dose once each week 1 hour before or 2 hours after a meal. The placebo was an identical-appearing lactose-free tablet.

Efficacy and safety were evaluated monthly in terms of signs or symptoms of MAC infection, adverse events, and intercurrent illnesses. A blood specimen for MAC culture was obtained at each monthly visit. Compliance was evaluated, and a calendar was used to keep a record of the day and date of each weekly dose. CD4 cell counts were determined every 6 months, and laboratory safety tests were performed monthly for 2 months and then bimonthly. Binaural audiograms were to be obtained within 1 month of the baseline visit, within 4 weeks of the final dose of study drug, and for any subject reporting hearing loss during the study.

Blood specimens for MAC cultures were collected in 8.3-mL sterile yellow top vacutainers (Becton Dickinson, Sparks, MD) containing sodium polyanetholesulfonate and were shipped to the National Jewish Center for Immunology and Respiratory Medicine in Denver for processing. The theoretical limit of detection was one viable organism per 8.3 mL of blood. Culture was performed in 7H12 BACTEC vials (Becton Dickinson), and the number of cfu/mL was quantified on plates with 7H11 agar. Identification to the species level was performed by a DNA-RNA hybridization technique (Gen-Probe, San Diego). MICs of clarithromycin and azithromycin were determined on Mueller-Hinton agar (pH 7.4) and in 7H12 broth (pH 7.4) [16].

The primary study end points were the development of MAC infection documented by culture of a specimen from a sterile tissue site, MAC bacteremia, or MAC infection—related symptoms including fever, night sweats, diarrhea, or weight loss unexplained by other etiologies and sufficient to warrant empirical therapy for MAC infection. The secondary study end points were the development of non-MAC bacterial infections (sinusitis, pneumonitis, bacteremia, and soft-tissue infection). The bacterial infections were defined by the investigators, and a positive culture (except for bacteremia) was not required.

Patients were to remain in the study for at least 18 months. Patients continued to receive the study drug weekly until they reached a primary study end point or died, unless they had treatment-related side effects or abnormalities revealed by laboratory studies that required study withdrawal, had an intercurrent infection requiring >4 weeks of therapy with a drug active against MAC, or had progression of AIDS to the extent that the subject’s disabilities precluded study continuation. Lack of compliance to the extent that a subject consistently failed to take >50% of the doses of study drug or attended <50% of the monthly follow-up visits was also a reason for study withdrawal.

**Statistical Analysis**

Sample size was based on an incidence of MAC bacteremia of 25% among the placebo group in 18 months. With 75 sub-
jectors in each group, a simple comparison of incidence rates yields a 50% power to detect a reduction of the infection rate to 12.5%. If treatment reduced the rate of infection to ≤8.39%, then the power would be ≥80%.

Subgroup analysis was performed with use of either the randomized treatment as the classification variable (intent-to-treat [ITT] analysis) or the actual treatment received as the classification variable (evaluable group). For the ITT analysis, all patients randomized and treated were included with the exception of those for whom baseline blood cultures were positive for MAC. Two separate ITT analyses were performed. The first (ITT-1) analysis included all study events through the end of therapy plus 30 days, while the second (ITT-2) analysis included all events through the last study follow-up visit. For the evaluable group, subjects for whom baseline blood cultures were positive for MAC or who had received ≤30 days of treatment were excluded. Events were excluded from the evaluable group analysis if they occurred ≤30 days after starting the study drug, ≥30 days after the last dose of the study drug, or after missing 30 consecutive days of the study drug.

Primary analyses were based on time to the event. Cox regression (proportional hazards model) was used to generate a P value and a hazard ratio (HR) for time to the event with 95% confidence intervals (SAS PROC PHREG, SAS Institute, Cary, NC). The Kaplan-Meier product limit method was used to generate a log rank, and a generalized Wilcoxon test was used to calculate time to the event.

The data capture window for symptoms associated with a MAC end point was from 60 days before the event through 30 days after the event. For the laboratory tests, the closest assessment within 180 days before the event or 90 days after the event was used.

A predetermined interim analysis was performed in August 1994 at an α value of .001. Results for time to the MAC event showed superiority of azithromycin over placebo at the significance level of P ≤ .05 but not at the prespecified level of P ≤ .001. Because of the interim analysis, statistical significance was judged at an α value of .049 to maintain an overall significance of .05. All P values were two-sided.

Additional sensitivity analyses were performed to determine the consistency of the primary analysis under other conditions. Covariate adjustments for the analysis of time to the MAC event included stratification by center and baseline CD4 cell count.

Results

Study Populations

Study enrollment began in June 1992 and continued through August 1994. Eighty-nine patients were randomized to receive azithromycin, and 93 were randomized to receive placebo. Two patients in the azithromycin group never received the study drug and were excluded from analysis. Two patients in the azithromycin group and four patients in the placebo group for whom blood cultures were positive for MAC at the baseline visit were also excluded from the ITT analysis. Three placebo recipients received the study drug for <30 days and were excluded from the evaluable analysis. Therefore, there were 85 and 86 patients in the azithromycin and placebo groups, respectively.

The baseline characteristics were similar between the two groups (table 1). Most patients were males from 24 to 44 years of age. The mean weight was 71.7 kg (range, 48–100 kg) for the azithromycin group and 70.6 kg (range, 46–103 kg) for the placebo group. The mean values for hemoglobin and alkaline phosphatase were similar at baseline, as were the median CD4 cell counts (43.9 vs. 44.3/mm³ in the azithromycin and placebo groups, respectively). The use of antiretroviral agents, prophylaxis for pneumocystis infection, and baseline opportunistic infections were also generally comparable between the two groups (table 2).

The mean duration of therapy was 400 days (range, 30–985 days) for the azithromycin group and 340 days (range, 36–1018 days) for the placebo group. The study was terminated early by the sponsor in May 1995 on the basis of a preliminary review of data from a separate study that raised ethical concerns for the placebo group. At the time of study termination, the most recently enrolled subject had been in the study for 8.5 months, and 120 subjects had met the predetermined study length of 18 months.

Disseminated MAC Infection

In the evaluable group, seven (8.2%) of 85 azithromycin recipients and 20 (23.3%) of 86 placebo recipients developed disseminated MAC infection (HR, 0.28; P = .002) (table 3).
Table 2. Baseline use of antiretroviral agents and prophylaxis for pneumocystis infection by patients with AIDS and CD4 cell counts of <100/mm³ who received azithromycin or placebo as prophylaxis for Mycobacterium avium complex infection.

<table>
<thead>
<tr>
<th>Agent</th>
<th>No. of patients</th>
<th>Azithromycin recipients (n = 89)</th>
<th>Placebo recipients (n = 91)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antiretroviral agent</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zidovudine</td>
<td>59</td>
<td>62</td>
<td></td>
</tr>
<tr>
<td>Didanosine</td>
<td>40</td>
<td>38</td>
<td></td>
</tr>
<tr>
<td>Zalcitabine</td>
<td>40</td>
<td>34</td>
<td></td>
</tr>
<tr>
<td>Stavudine</td>
<td>12</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Prophylaxis for pneumocystis infection</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trimethoprim-sulfamethoxazole</td>
<td>65</td>
<td>60</td>
<td></td>
</tr>
<tr>
<td>Dapsone</td>
<td>15</td>
<td>21</td>
<td></td>
</tr>
<tr>
<td>Pentamidine</td>
<td>31</td>
<td>33</td>
<td></td>
</tr>
</tbody>
</table>

NOTE. Some patients received more than one antiretroviral or prophylactic agent during the study period.

In the ITT-1 analysis (through 30 days after completion of therapy), nine (10.6%) of 85 azithromycin recipients vs. 22 (24.7%) of 89 placebo recipients developed disseminated MAC infection (HR, 0.34; P = .004). In the ITT-2 analysis (through the last follow-up visit), 13 (15.3%) of 85 azithromycin recipients vs. 27 (30.3%) of 89 placebo recipients developed disseminated MAC infection (HR, 0.41; P = .006) (figure 1). The absolute risk reduction for MAC infection in the evaluable group by azithromycin therapy was 15.1%, with a relative risk reduction of 65%. The number of treated patients needed to prevent one case of disseminated MAC infection was 6.6.

The diagnosis of disseminated MAC infection was based on blood cultures positive for MAC in 25 of the 27 episodes in the evaluable group. The mean cfu/mL was 1.0 for the azithromycin group and 3.5 for the placebo group. One patient in the azithromycin group and one patient in the placebo group had a clinical syndrome consistent with disseminated MAC infection and positive acid-fast staining of tissue but negative cultures (bone marrow and cystic [gallbladder] lymph node, respectively). In the ITT-1 analysis, there was one additional blood culture positive for MAC in each group. In addition, there was one azithromycin recipient for whom bone marrow biopsy revealed granulomas but culture was negative and there was one placebo recipient for whom stool culture was positive for MAC. Both of these patients were symptomatic. In the ITT-2 analysis, there were three additional empirical diagnoses (two azithromycin recipients and one placebo recipient); the remaining diagnoses were based on blood or bone marrow cultures positive for MAC. For those patients in the evaluable group who developed MAC infection, the median time to diagnosis was 269 days in the azithromycin group compared with 169 days in the placebo group.

When the occurrence of disseminated MAC infection was stratified by baseline CD4 cell count, the greatest risk reduction was provided for the lowest quartile of CD4 cell counts (CD4 cell count, ≤24/mm³). In this group, two (6.5%) of 31 azithromycin recipients vs. 10 (33.3%) of 30 placebo recipients devel-

Table 3. Incidence and hazard of Mycobacterium avium complex bacteremia in patients with AIDS and a CD4 cell count of <100/mm³ who received azithromycin or placebo prophylaxis.

<table>
<thead>
<tr>
<th>Analysis</th>
<th>Azithromycin recipients</th>
<th>Placebo recipients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of patients</td>
<td>No. with a positive culture</td>
</tr>
<tr>
<td>Evaluable</td>
<td>85</td>
<td>6²</td>
</tr>
<tr>
<td>Intent-to-treat-1³</td>
<td>85</td>
<td>7</td>
</tr>
<tr>
<td>Intent-to-treat-2³</td>
<td>85</td>
<td>9</td>
</tr>
</tbody>
</table>

* Based on Cox regression proportional hazards model and is the risk of bacteremia while receiving azithromycin compared with placebo.

² One isolate was later identified as Mycobacterium flavescens.

³ Through 30 days after the last dose of study drug.

⁴ Through the last follow-up visit.
Table 4. Distribution of breakthrough (first) *Mycobacterium avium* complex isolates from patients with AIDS and CD4 cell counts of <100/mm³ who received azithromycin or placebo prophylaxis, by MICs of azithromycin and clarithromycin that were determined on Mueller-Hinton agar and in 7H12 broth at pH 7.3–7.4.

<table>
<thead>
<tr>
<th>Testing medium/treatment group</th>
<th>No. of isolates by azithromycin MIC (µg/mL)</th>
<th>No. of isolates by clarithromycin MIC (µg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>4.0  8.0  16.0  32.0  64.0  Total</td>
<td>&lt;0.25  0.5  1.0  2.0  4.0  Total</td>
</tr>
<tr>
<td>Mueller-Hinton agar</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Azithromycin</td>
<td>0    0    1    1    3    5</td>
<td>0    0    0    4    1    5</td>
</tr>
<tr>
<td>Placebo</td>
<td>0    1    2    2    13   18</td>
<td>0    0    0    4    14   18</td>
</tr>
<tr>
<td>7H12 broth</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Azithromycin</td>
<td>0    5    0    0    0    5</td>
<td>0    4    1    0    0    5</td>
</tr>
<tr>
<td>Placebo</td>
<td>3    10   4    1    1    18</td>
<td>0    9    8    1    0    18</td>
</tr>
</tbody>
</table>

Disseminated MAC infection (RR, 0.19; 95% CI, 0.06–0.66). In the group with CD4 cell counts of 25–49/mm³, three (13.6%) of 22 azithromycin recipients and seven (28%) of 25 placebo recipients developed disseminated MAC infection (RR, 0.48; 95% CI, 0.15–2.08). Of note, five (18.5%) of the 27 cases of MAC bacteremia occurred in subjects with a CD4 cell count of >50/mm³ at baseline.

Almost all patients in both groups who developed disseminated MAC infection were symptomatic during a period from 60 days before the MAC event to 30 days after the event. In the evaluable group, all seven azithromycin recipients who developed MAC infection had fever and night sweats, and five of seven had weight loss of >5% of the baseline weight. In the placebo group, 19 of 20 patients had fever, night sweats, or weight loss.

For the two groups as a whole, the mean percentage of visits at which an individual patient complained of fever was lower for azithromycin recipients than for placebo recipients (9.6% vs. 16.5%, respectively; *P* < .05).

**Drug Susceptibility**

Of the breakthrough (first) MAC isolates, five from azithromycin recipients and 18 from placebo recipients were available for determination of susceptibility to azithromycin and clarithromycin. The MICs of azithromycin were ≤64 µg/mL on Mueller-Hinton agar and ≤32 µg/mL in 7H12 broth for all isolates. The MICs of clarithromycin were ≤4 µg/mL on Mueller-Hinton agar and ≤2 µg/mL in 7H12 broth for all isolates. The range of MICs was similar between the isolates from azithromycin and placebo recipients (table 4).

**Survival**

Through the last follow-up visit, there were 38 deaths in each group. Of the patients who died, four (10.5%) of 38 azithromycin recipients vs. 12 (31.6%) of 38 placebo recipients had a diagnosis of MAC infection preceding their death (*P* = .025). In the ITT-2 evaluation, the death rate at 1 year (16.5% vs. 22.5%, respectively) and at 18 months (28.2% vs. 33.7%, respectively) was lower among the azithromycin group than among the placebo group. These differences were not statistically significant; however, the power to detect a difference of 20% at an *α* value of .05 was only 11.9%.

For the patients who died, there was a trend for the median time from the baseline visit to death to be longer (462 vs. 357 days, respectively) and the time from diagnosis of disseminated MAC infection to death to be longer (287 vs. 187 days, respectively) for the azithromycin group than for the placebo group. However, none of these comparisons reached statistical significance. For deaths due to all causes, the results were similar for the two groups (figure 2). For the evaluable group, 11 (12.9%) of 85 azithromycin recipients died vs. 10 (11.6%) of 89 placebo recipients (HR, 1.04; *P* = .92). In the ITT-1 analysis, 13 (15.3%) of 85 azithromycin recipients died vs. 11 (12.4%) of 89 placebo recipients (HR, 1.02; *P* = .955).

**Other Infections**

For non-MAC bacterial infections, there were significantly fewer episodes of sinusitis (12 vs. 30 episodes per 100 patient-days) among azithromycin recipients vs. placebo recipients (HR, 0.40; 95% CI, 0.24–0.69; *P* = .001). In the ITT-1 analysis, 13 (15.3%) of 85 azithromycin recipients had a non-MAC infection vs. 14 (15.8%) of 89 placebo recipients (HR, 0.90; 95% CI, 0.56–1.45; *P* = .71).
years, respectively) and pneumonia (3 vs. 18 episodes per 100 patient years, respectively) in the azithromycin group than in the placebo group (table 5). For soft-tissue infections and bacteremia, there was a nonsignificant trend toward fewer events in the azithromycin group than in the placebo group.

There were three cases of toxoplamosis and two cases of cryptosporidiosis diagnosed during the study in the placebo group. There were no new diagnoses of either opportunistic infection in the azithromycin group.

Although all patients were receiving prophylaxis for *Pneumocystis carinii* pneumonia (PCP), azithromycin recipients had 11.5 episodes of PCP per 100 patient years compared with 17.2 episodes per 100 patient years in the placebo group (HR, 0.66; 95% CI, 0.29–1.52). Among those azithromycin recipients who were not receiving therapy with a sulfonamide (trimethoprim-sulfamethoxazole or dapsone), the incidence of PCP was 7.5 episodes per 100 patient years compared with 78.6 episodes per 100 patient years in the placebo group (HR, 0.09; 95% CI, 0.01–0.75; *P* = .001). We conducted a randomized, double-blind, placebo-controlled trial that demonstrated that azithromycin (1,200 mg once a week) can significantly decrease the incidence of disseminated MAC infection. The absolute risk reduction of disseminated MAC infection associated with azithromycin prophylaxis was 15.1% (incidence of disseminated MAC infection, 23.3% among the placebo group vs. 8.2% among the azithromycin group). The relative risk reduction was 65%. This effect was statistically significant whether the analysis was based on the actual treatment received (evaluable group) or on the randomized treatment (ITT analysis). The reduction of the incidence of disseminated MAC infection was seen whether the analysis was limited to 30 days after the last dose of the study drug (ITT-1 analysis) or through the last follow-up visit that was thought to be related to the study drug occurred in 71 (78.9%) of 90 azithromycin recipients and in 25 (27.5%) of 91 placebo recipients. In the azithromycin group, 52.2% of the patients had diarrhea, 32.2% had nausea, 26.7% had abdominal pain, and 6.7% had nausea associated with the study drug at least once during the study. Most of these events were mild to moderate and well tolerated. However, 6.6% of the abdominal pain episodes, 4.4% of the diarrheal episodes, and 2.2% of the nausea episodes were rated as severe by the patients.

Seven azithromycin recipients (8.2%) withdrew from the study because of drug intolerance (six, gastrointestinal intolerance; one, rash), and two placebo recipients (2.3%) withdrew from the study because of drug-related toxic effects (one, gastrointestinal intolerance; one, rash) (*P* = .14). The median time to study withdrawal was 112 days for the azithromycin group.

Abnormalities revealed by laboratory studies were relatively common in both groups during the study. For subjects for whom results of liver function tests were normal at baseline, fivefold elevations of aspartate aminotransferase levels were noted in 4.8% of azithromycin recipients vs. 2.4% of placebo recipients. Fivefold elevations of alanine aminotransferase levels from normal baseline values were noted in 5% of azithromycin recipients compared with none of the placebo recipients. There were two premature withdrawals from the study because of increased transaminase levels in the azithromycin group during the study. However, both withdrawals were thought to be unrelated to the study drug by the blinded investigators. For subjects with neutrophil counts within normal limits at baseline, counts of ≤500/mm³ were seen in two (8%) of 25 azithromycin recipients compared with none of 26 placebo recipients.

During the study, three azithromycin recipients and four placebo recipients complained of new hearing loss. One of the azithromycin recipients and all four of the placebo recipients had objective findings on binaural audiograms (decrease in air conduction levels of ≥10 dB). An equal number of patients in each group complained of new onset tinnitus. Overall, new or increased objective findings were noted on binaural audiograms for 15 patients in each group.

### Adverse Events and Laboratory Abnormalities

During the study, the most frequent toxic effect was gastrointestinal. At least one episode of a gastrointestinal toxic effect that was thought to be related to the study drug occurred in 71 (78.9%) of 90 azithromycin recipients and in 25 (27.5%) of 91 placebo recipients. In the azithromycin group, 52.2% of the patients had diarrhea, 32.2% had nausea, 26.7% had abdominal pain, and 6.7% had nausea associated with the study drug at least once during the study. Most of these events were mild to moderate and well tolerated. However, 6.6% of the abdominal pain episodes, 4.4% of the diarrheal episodes, and 2.2% of the nausea episodes were rated as severe by the patients.

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#### Table 5. Incidence and relative risk of non-MAC bacterial infections among patients with AIDS and CD4 cell counts of <100/mm³ who received azithromycin or placebo prophylaxis.

<table>
<thead>
<tr>
<th>Infection</th>
<th>No. of episodes per 100 patient years</th>
<th>Azithromycin recipients (n = 85)</th>
<th>Placebo recipients (n = 89)</th>
<th>Relative risk* (95% CI)</th>
<th><em>P</em> value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sinusitis</td>
<td>12</td>
<td>30</td>
<td>0.40 (0.19–0.81)</td>
<td>.010</td>
<td></td>
</tr>
<tr>
<td>Pneumonia</td>
<td>3</td>
<td>18</td>
<td>0.18 (0.05–0.64)</td>
<td>.008</td>
<td></td>
</tr>
<tr>
<td>Soft-tissue infection</td>
<td>25</td>
<td>34</td>
<td>0.73 (0.42–1.28)</td>
<td>.275</td>
<td></td>
</tr>
<tr>
<td>Bacteremia</td>
<td>3</td>
<td>6</td>
<td>0.52 (0.12–2.18)</td>
<td>.366</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>43</td>
<td>88</td>
<td>0.49 (0.33–0.73)</td>
<td>&lt;.001</td>
<td></td>
</tr>
</tbody>
</table>

*Refers to relative risk of infection while receiving azithromycin compared with placebo.

NOTE. MAC = *Mycobacterium avium* complex.
culosis to produce cross-resistance to rifampin [18]. Currently, the U.S. Public Health Service recommends either clarithromycin or azithromycin as the preferred prophylactic agent for prevention of MAC infections [19].

Clarithromycin at a dosage of 500 mg twice a day appears to be highly effective in preventing MAC infection. A large multicenter trial revealed a 69% reduction in the incidence of MAC infections and a significant survival benefit when clarithromycin prophylaxis was compared with placebo [20]. Of major concern was the fact that 11 (57.9%) of 19 of the breakthrough isolates were resistant to clarithromycin. Because there has been almost universal cross-resistance between clarithromycin and azithromycin [21], these isolates may prove unresponsive to subsequent macrolide therapy, which is currently the cornerstone of effective therapy for MAC infection.

A comparison of the placebo-controlled trial of clarithromycin [20] and the current study is made difficult by the use of different end points and statistical analyses. However, if a comparable statistical analysis (intention to treat through the last follow-up) is performed and comparable end points (culture-positive cases only) are used, the reduction in risk of MAC infection is quite similar for azithromycin and clarithromycin (73% and 69%, respectively).

The most profound impact of azithromycin on the prevention of disseminated MAC infection was in the group of patients with a CD4 cell count of <25/mm³ at baseline, for whom a fivefold reduction in the incidence of disseminated MAC events was seen. A twofold reduction in the incidence of disseminated MAC infection was seen among patients with CD4 cell counts from 25 to 49/mm³. Of note, 18.5% of all episodes of MAC bacteremia occurred in patients with a CD4 cell count of >50/mm³ at baseline.

Some investigators have reported that MAC bacteremia may be detected transiently without association with clinical disease [22]. In this study, 100% of the azithromycin recipients and 80% of the placebo recipients who developed MAC bacteremia had fever, night sweats, or weight loss during a period from 60 days before the MAC event to 30 days after the event.

The azithromycin failures may be due to poor drug absorption, noncompliance, drug resistance, or as yet undefined reasons. The actual cause of azithromycin failures remains unclear, but development of resistance does not appear to be the reason. Although the number of isolates was small and the results will clearly need confirmation with testing of more breakthrough isolates, there was no resistance noted in the isolates from patients receiving azithromycin. The MICs of clarithromycin for all five breakthrough isolates from azithromycin recipients were ≤4 µg/mL on Mueller-Hinton agar and ≤1 µg/mL in 7H12 broth, findings consistent with the MICs for wild-type isolates that have never been exposed to clarithromycin [16]. The MICs of clarithromycin for breakthrough isolates recovered during treatment of patients with disseminated MAC infection whose conditions are clinically worsening consistently are >256 µg/mL [21]. A similar low rate of resistance in breakthrough isolates recovered during azithromycin prophylaxis was noted in the study by Havlir et al. [15], in which only two (11%) of 18 isolates were resistant to macrolides.

The development of macrolide resistance during prophylaxis is a critical issue as the macrolides serve as the backbone of effective therapy for disseminated MAC infection. The U.S. Public Health Service has recommended that combination therapy should always include a macrolide. Since there is essentially complete cross-resistance between azithromycin and clarithromycin [21], loss of susceptibility by MAC due to prophylaxis with one macrolide would result in a marked reduction in the efficacy of any subsequent treatment of disseminated MAC infection.

In this study, prophylaxis with azithromycin did reduce the number of deaths preceded by MAC infection; however, it did not reduce the number of deaths due to all causes. Of the evaluable group, 11 of 85 azithromycin recipients died, and 10 of 86 placebo recipients died. The study design may have made the detection of a difference in mortality more difficult as this study was, from a practical standpoint, a comparison of close monitoring, of routine monthly blood cultures for early diagnosis of MAC, and of rapid institution of macrolide therapy vs. azithromycin prophylaxis. The study conditions were clearly different from routine clinical practice and may have made it more difficult to demonstrate an impact on mortality. Despite these circumstances, there was a trend to an increase in the time from study baseline to death (462 vs. 357 days) as well as a nonstatistically significant trend to lower mortality at 12 and 18 months for the azithromycin group.

The effect of azithromycin prophylaxis on deaths due to all causes cannot be answered by this study because it was powered only to detect a difference in MAC events. The study had only an 11.9% power to detect a 20% reduction in the number of deaths due to all causes at 18 months.

We noted a significant reduction in the incidence of presumed non-MAC bacterial infections in the azithromycin group, specifically pneumonia and sinusitis. These results are consistent with the excellent activity of azithromycin against the most common respiratory tract pathogens and success in the treatment of these clinical entities that has been demonstrated in numerous comparative clinical trials [11].

Although there were too few episodes of PCP in this trial to demonstrate a statistically significant reduction in the number of all cases of PCP, there was a significant reduction in the incidence of PCP by azithromycin prophylaxis for those patients who were not receiving trimethoprim-sulfamethoxazole or dapsone. This reduction in the incidence of PCP is consistent with findings from another study of azithromycin prophylaxis in which the incidence of PCP was 13% among the placebo group and 8.7% among the azithromycin group (HR, 0.56; P = .045) [23].

The most frequent drug-related toxic effect was gastrointestinal, a finding consistent with the well-described activity of azithromycin and other macrolides as agonists of motilin (which directly enhances gastric contractions). This finding is also consistent with data for 3,995 patients who received...
azithromycin therapy for a variety of indications in whom the most common side effects were diarrhea (3.6%), nausea (2.6%), and abdominal pain (2.5%) [24]. Despite the high incidence of gastrointestinal toxic effects, the number of patients who rated the toxic effects as severe was low, as was the number of study withdrawals. Four patients (4.4%) rated their diarrhea as severe, and six patients (6.6%) rated their abdominal pain as severe. Only six of the 85 azithromycin recipients withdrew from the study because of gastrointestinal intolerance. This low withdrawal rate may be related to the intermittent nature of the dosing regimen, which would make the side effect transient and allow empirical pretreatment with metoclopramide, glycopyrrolate, or loperamide hydrochloride depending on the particular side effect [25].

Because hearing loss has been reported during macrolide therapy for disseminated MAC infection [24, 26], baseline binaural audiograms were obtained for all patients, and repeated studies were performed for any complaints of hearing loss and after completion of the study. We found no evidence that prolonged (mean, 400 days) intermittent azithromycin prophylaxis resulted in audiological toxic effects.

The abnormalities revealed by laboratory studies that were noted in this study (increased transaminase levels and decreased neutrophil counts) were self-limited and did not result in serious clinical consequences or study withdrawal. The two azithromycin recipients who withdrew from the study prematurely because of increased transaminase levels both had abnormalities in liver function at baseline, and the investigators, who were blinded to the treatment group, did not believe that azithromycin was the cause of these abnormalities. In a large study of azithromycin therapy for a variety of indications, the only abnormalities revealed by laboratory studies that were found more often than 1% of the time were increased transaminase levels (1.7%), decreased leukocyte counts (1.1%), and decreased neutrophil counts (1.5%) [24]. These findings suggest that these abnormalities may be related to the study drug, and periodic assessment of these laboratory test results may be warranted.

In conclusion, azithromycin (1,200 mg once weekly) is safe and effective prophylaxis for disseminated MAC infection, death due to MAC infection, and respiratory tract infections in patients with AIDS and a CD4 cell count of <100/mm³.

Additional Clinical Investigators

In addition to the authors, the following clinical investigators participated in the study: K. Konkol and W. Williams (Fitzsimmons Army Medical Center, Aurora, CO); C. Decker (National Naval Medical Center, Bethesda, MD); M. Kortepeter, and K. McKee (Womack Army Medical Center, Fort Bragg, NC); and P. Joyce and C. Davis (Brooke Army Medical Center, Fort Sam Houston, TX).

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