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# Activities of Azithromycin and Clarithromycin against Nontuberculous Mycobacteria in Beige Mice

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**The comparative activities of azithromycin (AZI) and clarithromycin (CLA) were evaluated against nontuberculous mycobacteria in a murine model of disseminated infection. Four-week-old beige mice (C57BL/6J *bg^j/bg^j*) were infected intravenously with approximately $10^7$ viable *Mycobacterium kansasii, M. xenopi, M. simiae*, or *M. malmoense*. Treatment with AZI at 200 mg/kg, CLA at 200 mg/kg, ethambutol at 125 mg/kg, rifampin at 20 mg/kg, or clofazimine at 20 mg/kg of body weight was started 7 days postinfection, and the treatments were administered 5 days per week for 4 weeks. Control groups were sacrificed at the start and end of the treatments. Spleens and lungs were homogenized, and viable cell counts were determined by serial dilution and plating onto 7H10 agar. AZI and CLA had activities comparable to or better than that of rifampin, ethamutol, or clofazimine against these nontuberculous mycobacteria in the beige mouse test system. AZI at 200 mg/kg was more active than CLA at 200 mg/kg against organisms in the spleens for *M. xenopi* and *M. malmoense*. The activities of AZI and CLA were comparable against organisms in the spleens for *M. kansasii* and *M. simiae*. The activities of these two agents were comparable against organisms in the lungs for all four nontuberculous mycobacterial species. AZI or CLA in combination with other agents may be useful for the therapy of nontuberculous mycobacterial infections in humans.**

Diseases caused by the nontuberculous mycobacteria (NTM) appear to be increasing in prevalence (32, 36). This is due in part to immunosuppression in people who are transplant recipients, are undergoing cytotoxic or corticosteroid therapy, or have underlying human immunodeficiency virus infection (15, 22, 27, 33, 39).

*Mycobacterium kansasii* is a photochromogen that usually causes chronic lung infection resembling pulmonary tuberculosis. Cases of soft tissue or bone and joint infections are also reported (36, 37). Disseminated infections typically occur in people with underlying immunosuppression (2, 29). The recommended treatment regimen for infections caused by *M. kansasii* is a combination of rifampin (RIF), isoniazid, and ethambutol (EMB) (32, 36). RIF is generally considered the most active agent (1, 25).

*M. xenopi*, *M. simae*, and *M. malmoense* are infrequent human pathogens but also appear to be increasing in prevalence, particularly in certain geographic locations (22, 36, 39). These NTM species cause lymphadenitis or chronic pulmonary infection. The in vitro susceptibilities of these organisms and the results of chemotherapy have been variable (3, 14, 21).

Erythromycin has limited activity against mycobacteria and is used only against infections caused by susceptible strains of *M. chelonae* (31). Two new macrolide analogs, azithromycin (AZI) and clarithromycin (CLA), have enhanced in vitro activities against a number of NTM species, including *M. fortuitum*, *M. chelonae*, *M. avium* complex, and *M. kansasii* (4, 12, 13, 24, 35). AZI and CLA also have promising activities in murine models of infection with *M. avium* complex (MAC) (6, 9, 19) and *M. leprae* (11, 17).

The purpose of the present study was to evaluate the activities of AZI and CLA against *M. kansasii*, *M. xenopi*, *M. simiae*, and *M. malmoense* in the beige mouse test system. The activities of these new agents were compared with those of RIF, EMB, and clofazimine (CFZ).

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## MATERIALS AND METHODS

**Drugs.** AZI was provided by the Central Research Division, Pfizer, Inc., Groton, Conn. CLA was provided by Abbott Laboratories, Abbott Park, Ill. CFZ was provided by CIBA-GEIGY Pharmaceuticals, Summit, N.J. RIF and EMB were purchased from Sigma Chemical Co., St. Louis, Mo. AZI and CLA were dissolved in absolute ethanol and were subsequently diluted in distilled water prior to administration. RIF and CFZ were dissolved in dimethyl sulfoxide (DMSO) and were subsequently diluted in distilled water. EMB was dissolved in distilled water. The final concentration of ethanol or DMSO in the drug preparations was 0.5%. Drugs were freshly prepared each morning prior to administration.

**Mycobacterial isolates.** *M. kansasii* PIC was obtained as a pulmonary isolate from a patient with AIDS at the State University of New York Health Science Center, Syracuse. *M. xenopi* MUL was obtained as a pulmonary isolate from a patient at the State University of New York Health Science Center, Syracuse. The *M. simiae* isolate was kindly provided by Elizabeth Thompson, Laboratory of Pathology, San Antonio, Tex. The *M. malmoense* isolate was kindly provided by Margaret Heginbothom, Public Health Laboratory Service, Mycobacterium Reference Unit, University Hospital of Wales, Cardiff, United Kingdom.

The MICs of AZI and CLA were determined in Mueller-Hinton broth (pH 7.4) supplemented with 10% oleic acid-albumin-dextrose-catalase (OADC) enrichment (Difco Laboratories, Detroit, Mich.) (28). The MICs of RIF, EMB, and CFZ were determined in modified Middlebrook 7H10 broth (pH 6.6; 7H10 agar formulation with agar and malachite green omitted) supplemented with 10% OADC enrichment (5). Comparative MICs are given in Table 1.

**Medium.** Organisms were grown in modified Middlebrook 7H10 broth with 10% OADC enrichment–0.05% Tween 80

TABLE 1. MICs of the antimicrobial agents tested in the present study

| NTM isolate | MIC (μg/ml) | | | | |
|---|---|---|---|---|---|
| | RIF | EMB | CFZ | CLA | AZI |
| *M. kansasii* | 0.125 | 0.25 | 1 | 0.5 | 0.5 |
| *M. xenopi* | 0.03 | 4 | 0.03 | 0.03 | 1 |
| *M. simiae* | 1 | 4 | 0.5 | 4 | 8 |
| *M. malmoense* | 0.06 | 0.125 | 1 | 2 | 2 |

(30) on a rotary shaker at 37°C for 3 to 6 days. The culture suspension was diluted in modified 7H10 broth to yield 10 Klett units per ml (Klett-Summerson colorimeter; Klett Manufacturing, Brooklyn, N.Y.), or approximately 5 × $10^7$ CFU/ml. The size of the inoculum was determined by titration and counting from triplicate 7H10 agar plates (BBL Microbiology Systems, Cockeysville, Md.) supplemented with 10% OADC enrichment. The plates were incubated at 37°C prior to counting (3 weeks for *M. kansasii*, 4 weeks for *M. simiae* and *M. malmoense*, 6 weeks for *M. xenopi*).

**Infection studies.** Four- to 6-week-old beige (C57BL/6J $bg^j/bg^j$) mice, bred at our facility, were infected intravenously through a caudal vein. Mice of the same sex were used in separate experiments. Each mouse received approximately $10^7$ viable organisms suspended in 0.2 ml of modified 7H10 broth. There were six mice per group.

In all experiments, treatment was started 7 days postinfection and was administered by gavage 5 days per week for 4 weeks. The dose volume was 0.2 ml. A group of mice, designated early controls, was sacrificed at the start of treatment. A group of infected but untreated mice, designated late controls, was sacrificed at the end of treatment and was compared with the treated groups of mice. Animals were sacrificed by cervical dislocation 3 to 5 days after administration of the last dose of drug. Spleens and lungs were aseptically removed and were ground in a tissue homogenizer. The number of viable organisms was determined by titration on 7H10 agar.

**Statistical evaluation.** The viable cell counts were converted to logarithms, which were then evaluated by one- or two-variable analyses of variance. Statistically significant effects from the analyses of variance were further evaluated by the Tukey honestly significant difference test (18) to make pairwise comparisons among means. The results of the statistical evaluations are summarized below.

## RESULTS

**Infection study. (i) *M. kansasii*.** AZI at 200 mg/kg, CLA at 200 mg/kg, RIF at 20 mg/kg, or EMB at 125 mg/kg of body weight was given to female mice which had been infected with 7.8 × $10^6$ viable *M. kansasii*. Statistical analysis indicated that the increases in cell counts between the early and late control groups were significant for organisms in the lungs ($P < 0.01$) but not those in the spleens ($P > 0.05$) (Fig. 1).

The reductions in cell counts between the early control group and the group receiving RIF, AZI, or CLA were significant for organisms in the spleens ($P < 0.01$ for each). The reductions in organism cell counts in spleens between the late control group and each of the RIF, AZI, or CLA treatment groups were also significant ($P < 0.01$). There was no difference in activity against organisms in the spleens between groups receiving RIF, AZI, or CLA ($P > 0.05$). The difference in organism cell counts in the spleens between either

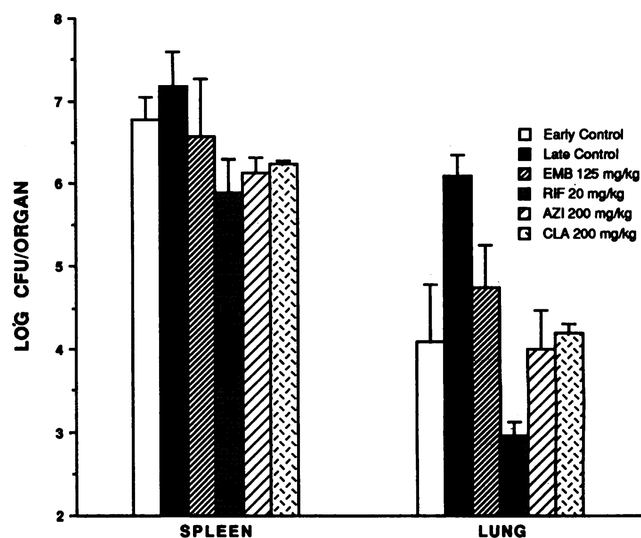


FIG. 1. Activities of antimicrobial agents against *M. kansasii*. Results are means for six mice per group. Error bars reflect standard deviations.

the early control group or the late control group and the EMB-treated group was not significant ($P > 0.05$ for each).

The reduction in cell counts between the early control group and the RIF-treated group was significant for organisms in the lungs ($P < 0.01$). The difference in organism cell counts in the lungs between the early control group and the group receiving either AZI or CLA was not significant ($P > 0.05$ for each). The reductions in organism cell counts in the lungs between the late control group and the groups receiving RIF, AZI, and CLA were significant ($P < 0.01$ for each). RIF was more active than either AZI or CLA against organisms in the lungs ($P < 0.01$). There was no difference in activity between AZI and CLA against organisms in the lungs ($P > 0.05$). The difference in organism cell counts in the lungs between the early control group and the EMB-treated group was not significant ($P > 0.05$). The difference in organism cell counts in the lungs between the late control group and the group receiving EMB was significant ($P < 0.01$).

**(ii) *M. xenopi*.** AZI at 200 mg/kg, CLA at 200 mg/kg, RIF at 20 mg/kg, or CFZ at 20 mg/kg was given to female mice which had been infected with 8.2 × $10^6$ viable *M. xenopi*. The differences in organism cell counts between the early control group and the late control group were significant for organisms in the lungs ($P < 0.01$) but not the spleens ($P > 0.05$) (Fig. 2).

The reduction in cell counts between either the early control or the late control group and all treatment groups was significant for organisms in the spleens ($P < 0.01$ for each). CFZ was the least active agent against organisms in the spleens. In the groups receiving RIF and CLA, there was no difference in the activities of the drugs against organisms in the spleens ($P > 0.05$). The reduction in organism cell counts in the spleens between groups receiving either RIF or CLA and the group receiving AZI was significant ($P < 0.01$).

The reduction in organism cell counts between the early control group and groups receiving either AZI or CLA was significant for organisms in the lungs ($P < 0.01$). There was no difference in organism cell counts in the lungs between the early control group and the CFZ-treated group ($P > 0.05$). The increase in organism cell counts in the lungs between the early control group and the RIF-treated group was significant ($P <$

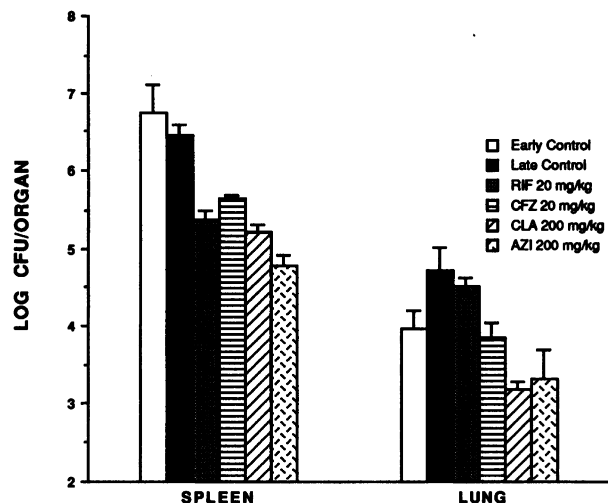


FIG. 2. Activities of antimicrobial agents against *M. xenopi*.

0.01); however, there was no difference in organism cell counts between the late control group and the RIF-treated group ($P > 0.05$).

**(iii) *M. simiae*.** AZI at 200 mg/kg, CLA at 200 mg/kg, RIF at 20 mg/kg, or CFZ at 20 m/kg was given to male mice which had been infected with $2.2 \times 10^7$ viable *M. simiae*. The difference between early and late control groups was significant for organisms in the spleens ($P < 0.01$) but not the lungs ($P > 0.05$) (Fig. 3).

Treatment with RIF, CFZ, AZI, or CLA reduced the organism cell counts in the spleens in comparison with the counts in the spleens of the early control group ($P < 0.01$ for each). There was no difference in organism cell counts in the spleens between the late control group and the RIF-treated group ($P > 0.05$). Treatment with CFA, AZI, or CLA reduced organism cell counts in the spleens in comparison with the counts in the spleens of the late control group ($P < 0.01$). CFZ was more active than AZI or CLA against organisms in the spleens ($P < 0.01$); however, there was no significant difference between treatment with AZI and CLA ($P > 0.05$).

Treatment with CFZ, AZI, or CLA reduced organism cell

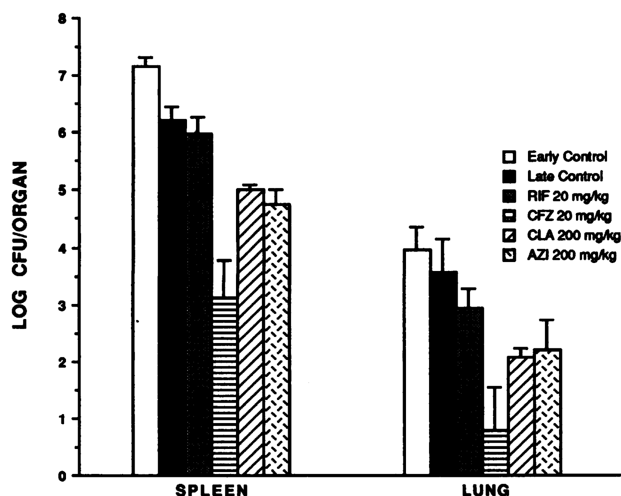


FIG. 3. Activities of antimicrobial agents against *M. simiae*.

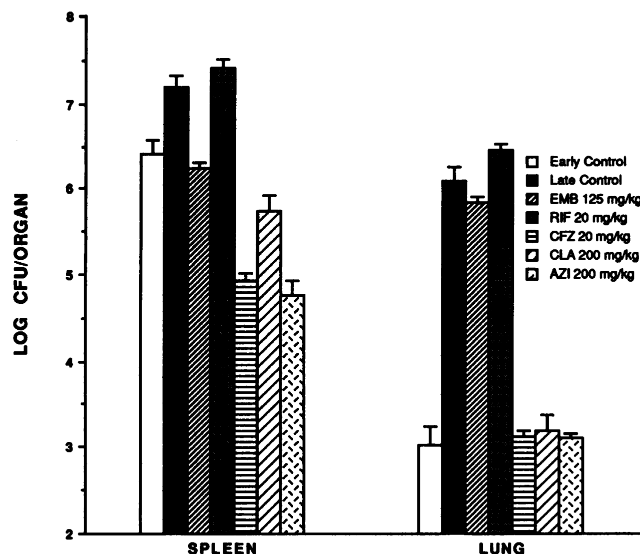


FIG. 4. Activities of antimicrobial agents against *M. malmoense*.

counts in the lungs compared with the counts in the lungs of either the early or the late control group ($P < 0.01$). CFZ was more active than AZI or CLA against organisms in the lungs ($P < 0.01$), and there was no significant difference in activity between AZI and CLA ($P > 0.05$). There was no difference in the organism cell counts in the lungs between either the early or the late control group and the RIF-treated group ($P > 0.05$).

**(iv) *M. malmoense*.** AZI at 200 mg/kg, CLA at 200 mg/kg, EMB at 125 mg/kg, RIF at 20 mg/kg, or CFZ at 20 mg/kg was given to female mice which had been infected with $6.8 \times 10^6$ viable *M. malmoense*. The increases in cell counts between early and late control groups were significant for organisms in the spleens and lungs ($P < 0.01$ for each) (Fig. 4).

Treatment with CFZ, AZI, or CLA reduced the organism cell counts in the spleens in comparison with those in the spleens of either the early or the late control group ($P < 0.01$). CLA was less active than CFZ or AZI against organisms in the spleens ($P < 0.01$), and there was no significant difference between CFZ and AZI ($P > 0.05$). Treatment with EMB did not reduce organism cell counts in the spleens in comparison with those in the spleens of the early control group ($P > 0.05$); however, the reduction in organism cell counts seen in the EMB-treated group in comparison with those seen in the late control group was significant ($P < 0.01$). The increase in organism cell counts in the spleens between the early control group and the RIF-treated group was significant ($P < 0.01$).

No treatment reduced cell counts in the lungs in comparison with the counts in the lungs of the early control group ($P > 0.05$). The increase in organism cell counts in the lungs between the early control group and the group receiving either EMB or RIF was significant ($P < 0.01$). Treatment with CFZ, AZI, or CLA reduced organism cell counts in the lungs of treated mice in comparison with the counts in the lungs of the late control group ($P < 0.01$). There was no significant difference in activity between CFZ, AZI, and CLA against organisms in the lungs ($P > 0.05$).

## DISCUSSION

MAC is the most common NTM species associated with disease in humans. Disease caused by this opportunistic organ-

ism includes cervical lymphadenitis and chronic progressive pulmonary infection. Disseminated infections with MAC were unusual until the late 1970s, but they have increased as more individuals became immunosuppressed because of solid organ transplants or newer cytotoxic therapies. The high degree of prevalence of disseminated MAC infection in patients with advanced human immunodeficiency virus infection has focused attention on the development of new antimycobacterial agents. AZI and CLA are promising new agents for the treatment of disseminated *M. avium* infection. The activities of AZI and CLA used as single agents in the treatment of disseminated MAC infection have been reported previously (8, 38).

Other NTM associated with lymphadenitis or chronic lung disease include *M. kansasii*, *M. xenopi*, *M. simiae*, and *M. malmoense*. Although people in certain geographic areas have higher incidences of lung disease caused by *M. kansasii*, *M. xenopi*, or *M. malmoense*, the relatively sporadic nature of disease caused by these NTM species makes it difficult to conduct randomized controlled trials to compare treatment regimens. Several retrospective and prospective studies of various treatment regimens for *M. kansasii* infections have provided a basis for treatment recommendations. However, there is inadequate information on which to make treatment recommendations for infections caused by *M. xenopi*, *M. simiae*, and *M. malmoense*. This is a concern because of increasing reports of disseminated infections with these organisms. Results of in vitro susceptibility testing have been variable, and the evaluation of antimicrobial agents in animal models of NTM infection has been limited (10, 23, 34). A correlation between in vitro susceptibility and clinical outcome has not been established for infections caused by these organisms.

AZI and CLA had activities comparable to that of RIF against organisms in the spleens of *M. kansasii*-infected mice. RIF was more active than AZI or CLA against organisms in the lungs. AZI and CLA were more active than EMB against organisms in the spleens and lungs.

AZI, CLA, CFZ, and RIF had activities against organisms in the spleens of *M. xenopi*-infected mice. AZI and CLA were more active than CFZ or RIF against organisms in the spleens and lungs. Dautzenberg et al. (7) reported the activities of CLA-containing regimens for the treatment of *M. xenopi* lung disease. Sputum conversion to negative occurred for 9 of 11 human immunodeficiency virus-negative individuals after 3 months of treatment. Other agents used in the treatment regimens included ofloxacin and ETM or CFZ, so the contribution of each individual agent is not clear.

CFZ, AZI, and CLA were more active than RIF against organisms in the spleens and lungs of *M. simiae*-infected mice. CFZ was the most active agent tested against this NTM isolate; however, the role of CFZ in the treatment of mycobacterial infections is not clear. We have noted the activity of CFZ against MAC and *M. tuberculosis* in murine models (6, 19, 20); however, CFZ did not appear to be active in a rhesus monkey model of *M. tuberculosis* infection (26). Ji et al. (16) noted a carryover effect of drug in suspensions of organs from mice treated with CFZ-containing regimens for 12 weeks; the cultures produced false-negative results. Evaluation of the activity of CFZ against human clinical disease may be necessary to judge its role as an antimycobacterial agent.

AZI, CFZ, and CLA were more active than EMB or RIF against organisms in the spleens and lungs of *M. malmoense*-infected mice. However, neither CFZ, AZI, nor CLA decreased the initial population of organisms in the lungs of *M. malmoense*-infected mice. The poor activity of RIF is difficult to explain in light of the low MIC of RIF in vitro for this *M. malmoense* isolate.

AZI at 200 mg/kg was more active than CLA at 200 mg/kg against organisms in the spleens for *M. xenopi* and *M. malmoense*. The activities of these agents were comparable against organisms in the spleens for *M. kansasii* and *M. simiae*. The activities of AZI and CLA were comparable against organisms in the lungs for all four NTM species.

AZI and CLA had promising activities against the NTM species tested in the present study in the beige mouse test system. Further study of these NTM species in the beige mouse system would be useful for evaluating the activities of single agents and drug combinations prior to their application in the treatment of human disease. It is likely that AZI or CLA in combination with other agents will be useful for the therapy of NTM infections in humans.

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