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Letter to the Editor

Mycobacterium avium Strains Resistant to Clarithromycin and Azithromycin

Heifets and colleagues recently reported on *Mycobacterium avium* strains resistant to macrolides. (1). I realize that the report was written by laboratory scientists, but perhaps they can consult their clinical colleagues to provide some necessary data regarding the patients from whom these strains were isolated.

Were these patients located in Denver, either at the Health Sciences Center or the National Jewish Center? Had they all failed previous attempts at drug treatment? Were they all on monotherapy with one of these macrolides? Did all 39 patients have AIDS?

The emergence of resistance was predictable on the basis of extensive experience with monotherapy with many antituberculosis drugs, beginning with streptomycin in 1945. In all probability, the macrolide treatment represented a last desperate attempt at salvage, but it would be highly desirable to have it confirmed in the journal that this was the case and that the patients were made fully aware of the consequences of monotherapy.

REFERENCE

1. **Heifets, L., N. Mor, and J. Vanderkolk.** *Mycobacterium avium* strains resistant to clarithromycin and azithromycin. Antimicrob. Agents Chemother. **37**:2364–2370.

Emanuel Wolinsky, M.D.
Division of Infectious Disease
MetroHealth Medical Center
2500 MetroHealth Drive
Cleveland, Ohio 44109-1998

Author's Reply

Though our article is not a report on the clinical efficacy of clarithromycin, we have provided detailed information on the bacteriological response to therapy in 39 AIDS patients whose isolates were the subject of our study (4). These AIDS patients were among a total of 154 enrolled in a clarithromycin clinical trial organized in 1991 by the AIDS Clinical Trials Group (ACTG) and Abbott Laboratories. The outcome of this trial was presented previously (1), and a full report has been submitted for publication (2).

The last paragraph of our article states that the "fall-and-rise" phenomenon and the emergence of drug resistance as a result of monotherapy were known only from observations with tuberculosis patients. The emergence of drug resistance as a result of monotherapy in patients with *M. avium* has not been previously reported and therefore was not considered predictable by those who organized the first clinical trials. For patients with *M. avium* infection the concept of multidrug therapy is to overcome the "natural" drug resistance of these organisms rather than to prevent the emergence of drug resistance, which is the aim in tuberculosis therapy. Moreover, the effectiveness of the antituberculosis regimens against *M. avium* has never been confirmed in controlled clinical trials.

Patients with AIDS acquire *M. avium* infection at the terminal period of their lives, and usually there is not enough time to try various changes in therapy. According to the results of the first controlled trial conducted in France (3), in 1991 clarithromycin did not represent the last desperate attempt but rather was the best chance to improve the quality of life of AIDS patients suffering from disseminated *M. avium* infection. In this trial, clarithromycin was highly effective and the conventional antituberculosis regimen was not; no emergence of resistance to clarithromycin was observed. In the first indications that resistance to clarithromycin may emerge were obtained *after* the first ACTG study (1, 2), in which most of the patients, after successful treatment of their *M. avium* infections with clarithromycin, died from concurrent conditions before relapse of the bacteremia and drug resistance could occur. Therefore, for our analysis we selected informaton on only those patients who survived for more than 150 days to reach the relapse state. This analysis provided the first evidence that the fall-and-rise phenomenon can occur and is predictable in patients with *M. avium* infection undergoing monotherapy with a drug which is effective against these organisms. It was also shown that the time lapse in this case is much greater than that for tuberculosis monotherapy. As with tuberculosis, combined drug regimens may prevent resistance to clarithromycin, and a search for effective companion drugs is among the urgent needs of our time (5).

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L. Heifets
N. Mor
J. Vanderkolk
National Jewish Center for Immunology and Respiratory Medicine
1400 Jackson Street
Denver, Colorado 80206