Successful Short-Term Suppression of Clarithromycin-Resistant Mycobacterium avium Complex Bacteremia in AIDS

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During a randomized study of clarithromycin plus clofazimine with or without ethambutol in patients with AIDS and Mycobacterium avium complex (MAC) bacteremia, eight participants received additional antimycobacterial drugs following the detection of a clarithromycin-resistant isolate (MIC, >8 µg/mL). A macrolide (seven received clarithromycin, one azithromycin) and clofazimine were continued; additional treatment included various combinations of ethambutol, ciprofloxacin, amikacin, and rifabutin. After the detection of a resistant isolate and before receipt of additional antimycobacterials, the median peak MAC colony count in blood was 105 cfu/mL (range, 8–81,500 cfu/mL). After additional antimycobacterials, the median nadir MAC colony count was 5 cfu/mL (range, 0–110 cfu/mL). Five (63%) of eight patients had a ≥1 log₁₀ decrease, including two who achieved negative blood cultures; all of these responses occurred in patients originally assigned to clarithromycin plus clofazimine. Treatment of clarithromycin-resistant MAC bacteremia that emerges during clarithromycin-based treatment can decrease levels of bacteremia and transiently sterilize blood cultures.
Table 1. Treatment response for eight patients with *Mycobacterium avium* complex (MAC) bacteremia who received additional antimycobacterial agents after the isolation of clarithromycin-resistant MAC.

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Initial antimycobacterial therapy</th>
<th>Subsequent antimycobacterial therapy</th>
<th>Peak MAC colony count in blood (cfu/mL)</th>
<th>Nadir MAC colony count in blood (cfu/mL)</th>
<th>Duration of response* (weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Clm-Clof</td>
<td>Clm-Clof-Eth-Cpfx</td>
<td>16</td>
<td>20</td>
<td>8</td>
</tr>
<tr>
<td>2</td>
<td>Clm-Clof</td>
<td>Azm-Clof-Eth</td>
<td>12</td>
<td>20</td>
<td>69</td>
</tr>
<tr>
<td>3</td>
<td>Clm-Clof</td>
<td>Clm-Clof-Eth-Cpfx</td>
<td>12</td>
<td>28</td>
<td>490</td>
</tr>
<tr>
<td>4</td>
<td>Clm-Clof</td>
<td>Clm-Clof-Eth-Cpfx-Rib</td>
<td>12</td>
<td>28</td>
<td>81,500</td>
</tr>
<tr>
<td>5</td>
<td>Clm-Clof</td>
<td>Clm-Clof-Cpfx-Rib</td>
<td>16</td>
<td>24</td>
<td>630</td>
</tr>
<tr>
<td>6</td>
<td>Clm-Clof</td>
<td>Clm-Clof-Eth-Cpfx</td>
<td>16</td>
<td>32</td>
<td>19</td>
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<tr>
<td>7</td>
<td>Clm-Clof-Eth</td>
<td>Clm-Clof-Eth-Amik</td>
<td>24</td>
<td>24</td>
<td>12</td>
</tr>
<tr>
<td>8</td>
<td>Clm-Clof-Eth</td>
<td>Clm-Clof-Eth-Cpfx</td>
<td>24</td>
<td>24</td>
<td>140</td>
</tr>
</tbody>
</table>

NOTE. Amik = amikacin; Azm = azithromycin; Clof = clofazimine; Clm = clarithromycin; Cpfx = ciprofloxacin; Eth = ethambutol; Rib = rifabutin.
* Documented period of time MAC colony count remained ≥1 log$_{10}$ lower than peak MAC colony count after additional antimycobacterials.

**Results**

All subjects initially had clarithromycin-susceptible isolates. Twenty-seven (34%) of 80 evaluable patients had a resistant MAC isolate detected in blood during the study. Of these, eight (six in the two-drug arm and two in the three-drug arm) received additional antimycobacterials after the detection of a resistant isolate. Resistance occurred later in the two subjects receiving clarithromycin/clofazimine/ethambutol (24 weeks) than in the six receiving clarithromycin/clofazimine (12–16 weeks), similar to the results for the study as a whole [3].

Seven of the eight patients who received additional antimycobacterials had achieved negative blood cultures before isolation of resistant MAC. A macrolide (clarithromycin in seven, azithromycin in one) was continued in all patients. Amended regimens included various combinations of ethambutol, ciprofloxacin, amikacin, and rifabutin (table 1). After the detection of a resistant isolate and before the introduction of additional antimycobacterial drugs, the median peak colony count in blood was 105 cfu/mL (range, 8–81,500 cfu/mL). Bacteremia decreased at least transiently in all eight subjects. After additional antimycobacterials, the median nadir colony count was 5 cfu/mL (range, 0–110 cfu/mL). Five (63%) of eight had a ≥1 log$_{10}$ decrease; all of these responses occurred in patients originally assigned to the clarithromycin/clofazimine arm. Two of these five responders (two of eight overall, 25%) again achieved negative blood cultures, but both eventually relapsed (patients 1 and 4). Three (37%) of eight did not have a ≥1 log$_{10}$ decrease in MAC colony count. The two subjects whose initial therapy consisted of clarithromycin/clofazimine/ethambutol (patients 7 and 8) and one who initially received clarithromycin/clofazimine (patient 3) had only transient responses to additional antimycobacterials.

**Discussion**

Our results demonstrate that it is possible to reduce MAC bacteremia in persons with AIDS who develop rebound bacteremia with clarithromycin-resistant isolates during therapy with clarithromycin. Drug options for these persons remain limited, however, and many patients are at an advanced stage of HIV disease when resistance develops and may not be able to tolerate additional antimycobacterials.

Clarithromycin-resistant MAC bacteremia may occur during relapses of treatment [3] or failures of prophylaxis [7, 8] for MAC in AIDS patients. Although our study did not include any patients with clarithromycin-resistant MAC bacteremia that developed during prophylaxis, our results suggest that treatment of such patients is likely to be at least partially successful.

The role of continuing macrolide therapy in patients who have developed clarithromycin-resistant MAC bacteremia is unclear, but all of our patients continued to receive a macrolide. Lending support for this practice is the finding that at the time of autopsy of patients who died while receiving clarithromycin-based treatment regimens for MAC bacteremia, both clarithromycin-susceptible and clarithromycin-resistant MAC are present in tissues [9]. Although our practice is to continue macrolides if they are being well-tolerated, a randomized trial will be required to examine the value of this strategy.

The best microbiological responses occurred in the subjects whose initial therapy for bacteremia did not include ethambutol. Five of these six had ethambutol added after the emergence of clarithromycin resistance. Thus, ethambutol may have been essential to the improved response. Ethambutol had modest activity as monotherapy against MAC [10]; it reduced bacteriologic relapse and delayed the development of clarithromycin resistance in AIDS patients with MAC [3]. The two patients whose initial treatment included ethambutol had a poorer response to additional antimycobacterial drugs. In both, only a single agent was added to their regimens. Most patients with MAC bacteremia will have already been treated with ethambutol [1–4], suggesting that responses may be poor because of the absence of other potent drugs that could be used to treat relapses.
Ciprofloxacin may have contributed to bacteriologic responses. It was added to the regimen in six subjects, including four whose MAC colony counts in blood fell by ≥1 log_{10} and the two patients who achieved negative blood cultures. Ciprofloxacin has been used in combination with other non-macrolide agents with modest success for treatment of MAC [1, 11], but no data exist regarding its relative contribution to combination therapy, and it has not been studied as monotherapy for this disease.

The role of rifabutin in macrolide-based treatment of MAC bacteremia has not been well-defined. Only two of our patients received rifabutin. Because serum levels of clarithromycin are reduced when coadministered with rifabutin [12], and uveitis has been associated with use of the combination [13], this combination should be used with caution until data from ongoing comparative trials are reported.

Sustained complete responses (persistently negative cultures) were not achieved, although one patient had clearance of bacteremia for 20 weeks. However, this study was done before the availability of HIV-1 protease inhibitors. Highly active antiretroviral therapy, along with combinations of antimycobacterials active against MAC, may improve immunity and reduce tissue burdens of MAC sufficiently to eradicate MAC infection before the emergence of clarithromycin-resistant isolates. However, some patients may still develop clarithromycin-resistant MAC while receiving therapy. On the basis of these data, we recommend the addition of at least two agents with activity against MAC when resistance to clarithromycin causes relapses, along with highly active antiretroviral therapy.

References