Superiority of Enviomycin or Streptomycin over Ethambutol in Initial Treatment of Lung Disease Caused by Mycobacterium avium Complex*

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The rate of sputum conversion (continuously negative cultures for six months or more) was compared among four regimens given to 83 patients with moderately advanced, cavitary lung disease caused by Mycobacterium avium complex untreated previously. The regimens of rifampin + isoniazid + enviomycin and rifampin + isoniazid + streptomycin appeared to be superior to the regimen of rifampin + isoniazid + ethambutol. No statistically significant difference was observed between the regimens rifampin + isoniazid + enviomycin and rifampin + isoniazid + streptomycin. (Chest 1989; 95:1056-58)

Pulmonary disease caused by Mycobacterium avium complex is frequently difficult to cure. The difficulty is probably due to the insensitivity of M avium complex strains to the majority of antituberculosis drugs and due to an immunocompromised state of patients. The second possibility is considered from a fact that, although all persons inhale environmental mycobacteria including M avium complex, only a few people become infected. The chemotherapy of lung disease caused by M avium complex is a difficult problem, but recently we have made some advances. Ahn et al noticed that, as in tuberculosis, strong chemotherapy should be used in the initial treatment, because failure of the initial treatment makes further treatments difficult. Tsukamura observed that the failure of sputum conversion can give rise to the emergence of drug-resistant bacteria in the treatment of disease caused by M avium complex. Furthermore, it was shown that two kinds of strains occur: one naturally highly resistant to the majority of drugs, and another relatively susceptible to it. A few retrospective studies dealing with efficacy of chemotherapy have been made recently. Tsukamura and Ichiyama demonstrated that the regimens rifampin + isoniazid + streptomycin and rifampin + isoniazid + enviomycin were superior to the regimen of streptomycin + isoniazid + p-aminosalicylate. This finding showed that the regimens including rifampin and streptomycin or enviomycin are more effective in the treatment. However, the regimen of rifampin + isoniazid + ethambutol could not be shown as useful as the other two regimens including streptomycin or enviomycin. Thus, the present study has been designed to compare the regimens including streptomycin or enviomycin with the regimen including ethambutol and to compare the regimen including streptomycin with the regimen including enviomycin.

Materials and Methods

Patients

The patients who were admitted to this hospital during the period 1980-1987 (eight years) became the subjects of the study and were restricted to those who met the following conditions: the patients were limited to those previously untreated by any antituberculosis drugs and hospitalized for more than six months. The reason only hospitalized patients were the subjects of observation was to confirm the regularity of drug administration and to make sure of various examinations. The patients were followed up, at minimum, for one year, including the observation made in the outpatient clinic. All 83 patients evaluated in this study showed moderately advanced, cavitary disease (The NTA classification, 1969; the cavitary lesion was limited in dimension to one lobe or two lobes). Patients with far-advanced disease were omitted to make similar background conditions. The age and sex of the patients are shown in Table 1.

Diagnosis

The diagnosis was made based on simultaneous occurrence of two events: a new cavitary lesion on the chest roentgenogram and two or more isolations of mycobacteria belonging to the M avium complex by monthly sputum examination made in the initial three months (the criteria are different in the presence of a sclerotic cavitary lesion). For cultivation of acid-fast bacteria, Tween egg medium was used.

Treatment

Medical treatment was carried out according to the physician's preference. Four regimens were used: 1) rifampin + isoniazid + streptomycin; 2) rifampin + isoniazid + enviomycin (tuberculosis-calcinin-N); 3) rifampin + isoniazid + ethambutol; 4) rifampin + isoniazid.


**RESULTS**

The results are shown in Table 1. The regimen of RFP + INH + EVM gave the highest rate of sputum conversion: 93 percent. This was followed by the regimen of RFP + INH + SM, which gave 74 percent conversion. The rates of the regimens of RFP + INH + EB and RFP + INH were inferior to the above two. The regimens of RFP + INH + EVM and RFP + INH + SM were superior to the regimen of RFP + INH + EB showing statistically significant differences by the chi-square test with Yates' correction (p<0.05 percent). There was no statistically significant difference in rate between the regimens RFP + INH + EVM and RFP + INH + SM (Table 2). The rate of disappearance of the cavity did not differ among the four regimens.

**DISCUSSION**

In a previous paper, we reported that the regimens of RFP + INH + EVM and RFP + INH + SM were, with statistically significant difference, superior to the regimen of SM + INH + PAS (p-aminosalicylate) for use in initial treatment of disease caused by *M avium* complex. This finding showed that the regimens including RFP and SM or EVM are more effective, in spite of general belief that *M avium* complex is resistant to most drugs. However, the efficacy of EB was not clear when compared with the above two regimens. In the present study, the regimen of RFP + INH + EB was shown to be inferior to the regimens of RFP + INH + SM and RFP + INH + EVM. Furthermore, unexpectedly, the regimen of RFP + INH + EB could not be shown as superior to the regimen of RFP + INH. Such probable low efficacy of EB is understood from our previous observations showing that *M avium* complex strains were more resistant to EB than other nonpathogenic mycobacteria. However, the result does not mean that EB is entirely ineffective. There is some evidence suggesting that this drug was clinically effective.

Chemotherapy of lung disease caused by *M avium* complex is usually begun in a stage in which the species identification is not yet given. Patients with positive smear or culture are treated as those with tuberculosis. Therefore, in this stage, we must consider the possibility that the causative organism is *M avium* complex. We recommend using a regimen more effective for *M avium* complex infection, either regimen RFP + INH + EVM or RFP + INH + SM, or, as recommended by Ahn et al., a four-drug regimen of RFP + INH + SM + EB. Since the use of a four-drug regimen for patients with moderately advanced lesions is not common in this country, we prefer to use the regimen of RFP + INH + EVM, as EVM has no serious side effect as have SM and EB. The regimen of RFP + INH + EVM was shown to be as effective as the regimens of RFP + INH + SM and RFP + INH + EB in the initial treatment of pulmonary tuberculosis.

In this study, we observed the rate of disappearance of cavities. The rate was only 22 percent in all 83 patients observed. The rate is much lower than the rate of sputum conversion: 64 percent. Previously, we reported that, in tuberculous patients, the cavity closure occurred in most patients who attained sputum conversion, whereas it occurred infrequently in pa-

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**Table 1—Rates of Sputum Conversion and Disappearance of Cavity, and Sex and Age of Patients**

<table>
<thead>
<tr>
<th>Regimen</th>
<th>No. Patients</th>
<th>M/F Ratio</th>
<th>Average Age (years)*</th>
<th>Rate of Sputum Conversion % (No.)</th>
<th>Rate of Disappearance of cavity % (No.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RFP + INH + EVM</td>
<td>14</td>
<td>8:6</td>
<td>64.8 ± 14.9</td>
<td>93 (13/14)</td>
<td>36 (5/14)</td>
</tr>
<tr>
<td>RFP + INH + SM</td>
<td>27</td>
<td>19:8</td>
<td>53.3 ± 17.4</td>
<td>74 (20/27)</td>
<td>33 (9/27)</td>
</tr>
<tr>
<td>RFP + INH + EB</td>
<td>30</td>
<td>25:5</td>
<td>60.9 ± 13.4</td>
<td>50 (15/30)</td>
<td>10 (3/30)</td>
</tr>
<tr>
<td>RFP + INH</td>
<td>12</td>
<td>5:6</td>
<td>63.8 ± 14.7</td>
<td>42 (5/12)</td>
<td>8 (1/12)</td>
</tr>
<tr>
<td>Total</td>
<td>83</td>
<td>58:25</td>
<td>59.5 ± 15.2</td>
<td>64 (53/83)</td>
<td>22 (18/83)</td>
</tr>
</tbody>
</table>

*Mean ± standard deviation.

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**Table 2—Statistical Comparison of Rate of Sputum Conversion among Four Regimens**

<table>
<thead>
<tr>
<th>Regimens Compared</th>
<th>Rate of Sputum Conversion</th>
<th>Statistical Significance*</th>
</tr>
</thead>
<tbody>
<tr>
<td>RFP + INH + EVM</td>
<td>13/14</td>
<td>5.84 (p&lt;0.05%)</td>
</tr>
<tr>
<td>RFP + INH + EB</td>
<td>15/30</td>
<td>2.53 (p&lt;0.05%)</td>
</tr>
<tr>
<td>RFP + INH + SM</td>
<td>20/27</td>
<td>1.04 (p&gt;0.05%)</td>
</tr>
<tr>
<td>RFP + INH + EVM</td>
<td>20/27</td>
<td>5.73 (p&lt;0.05%)</td>
</tr>
<tr>
<td>RFP + INH + SM</td>
<td>20/27</td>
<td>2.51 (10%&lt;p&lt;0.05%)</td>
</tr>
<tr>
<td>RFP + INH</td>
<td>5/12</td>
<td>0.02 (p&gt;0.50%)</td>
</tr>
</tbody>
</table>

*Tested by the χ² test with Yates' correction (degree of freedom, 1). The value of the χ² is shown in the table.
tients with disease caused by *M avium* complex. The difference in rate of disappearance of the cavity between tuberculosis and disease caused by *M avium* complex seems to correlate with a fact that, in the *M avium* complex disease, real eradication of causative organisms is difficult; in spite of the occurrence of superficial sputum conversion, the bacteria may remain in the cavity wall or the repair of the cavity is difficult because of an immunocompromised state of the host. These possibilities may explain the fact that relapse occurs often in lung disease caused by *M avium* complex.

In conclusion, EVM or SM seemed to be superior to EB in the treatment of pulmonary disease caused by *M avium* complex.

REFERENCES


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