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In Vitro Activity of BAY 12-8039, a New Fluoroquinolone, against Mycoplasmas

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The in vitro activity of the fluoroquinolone BAY 12-8039 against 66 strains of different mycoplasma species and 30 strains of Ureaplasma urealyticum was compared with those of three other antimicrobial agents. BAY 12-8039 at 0.5 μg/ml inhibited 100% of all the mycoplasmal and ureaplasmal strains tested. The minimal bactericidal concentrations of BAY 12-8039 increased only two- to eightfold compared to the MICs. Furthermore, they were comparable to those of sparfloxacin and lower than those of doxycycline and clarithromycin.

BAY 12-8039 is a new 8-methoxyfluoroquinolone with potent activity against both gram-negative and gram-positive bacteria (9) and anaerobes (1). The various fluoroquinolones show different levels of activity against mycoplasmas. In this study, the activity of BAY 12-8039 against different mycoplasma species found in humans was compared with those of sparfloxacin, doxycycline, and clarithromycin.

(This work was presented in part at the 36th Interscience Conference on Antimicrobial Agents and Chemistry, New Orleans, La., 15 to 18 September 1996.)

Thirty-two strains of Mycoplasma pneumoniae (31 clinical respiratory isolates and one reference strain, FH), 9 strains of Mycoplasma fermentans (six clinical strains and three reference strains, PG18, K7, and incognitus), 7 strains of Mycoplasma genitalium (six clinical isolates and one reference strain, G37), 2 strains of Mycoplasma penetrans (one urethral isolate and one reference strain, GTU-54), and 16 strains of Mycoplasma hominis (15 clinical isolates and one reference strain, PG21) were tested. An additional group of eight M. hominis fluoroquinolone-resistant mutants, obtained from the reference strain PG21 by stepwise selection on increasing concentrations of various fluoroquinolones (3), was studied. For Ureaplasma urealyticum, 30 strains divided into two groups, i.e., 15 doxycycline-susceptible strains (12 clinical isolates and three reference strains, serotypes 1, 2, and 8) and 15 doxycycline-resistant strains (14 clinical isolates and one reference strain, serotype 9), were studied. The following antimicrobial agents were provided by the indicated manufacturer: BAY 12-8039 (Bayer Pharma, Puteaux, France), sparfloxacin (Rhoâˆš®ne-Poulenc-Rorer, Vitry-sur-Seine, France), doxycycline (Pfizer, Orsay, France), and clarithromycin (Abbott, Rungis, France).

Susceptibility testing of M. pneumoniae, M. hominis, M. fermentans, M. genitalium, and M. penetrans was performed by an agar dilution method on Hayflick modified medium (2) inoculated with 108 to 109 color-changing units of bacteria and incubated at 37°C in the presence of 5% carbon dioxide. The final concentrations of antibiotics tested were 0.015 to 32 μg/ml. The MIC was read as the lowest concentration of each drug completely inhibiting growth, when visible growth could be seen on the control plate without antibiotic, generally at 2 to 4 days for M. hominis, M. fermentans, and M. penetrans, at 4 days for M. pneumoniae, M. genitalium, and M. penetrans.

<table>
<thead>
<tr>
<th>Organism (no. of strains tested)</th>
<th>MIC (μg/ml)</th>
<th>MBC (μg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BAY 12-8039</td>
<td></td>
<td></td>
</tr>
<tr>
<td>M. pneumoniae (32)</td>
<td></td>
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<tr>
<td>Doxycycline</td>
<td>0.06–0.12</td>
<td>0.12 0.12 0.25</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>≤0.015–0.06</td>
<td>0.06 0.06 0.25</td>
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<tr>
<td>M. genitalium (7)</td>
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<tr>
<td>BAY 12-8039</td>
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<td>0.25</td>
</tr>
<tr>
<td>Doxycycline</td>
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<td>4</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>≤0.015–0.03</td>
<td>0.25</td>
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<tr>
<td>M. hominis (16)</td>
<td></td>
<td></td>
</tr>
<tr>
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<td>0.06 0.06</td>
<td>0.06 0.25</td>
</tr>
<tr>
<td>Doxycycline</td>
<td>≤0.015–16</td>
<td>16 2</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>&gt;32 &gt;32 &gt;32 ND</td>
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</tr>
<tr>
<td>M. fermentans (9)</td>
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<tr>
<td>BAY 12-8039</td>
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<td>0.03</td>
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<tr>
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<tr>
<td>Clarithromycin</td>
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<td>M. penetrans (2)</td>
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<td>Clarithromycin</td>
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<tr>
<td>U. urealyticum (doxycycline susceptible) (15)</td>
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<td></td>
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<tr>
<td>BAY 12-8039</td>
<td>0.12–0.5</td>
<td>0.25 0.25 1</td>
</tr>
<tr>
<td>Sparfloxacin</td>
<td>0.25</td>
<td>0.25 0.25 1</td>
</tr>
<tr>
<td>Doxycycline</td>
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<td>0.12 0.5 16</td>
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<tr>
<td>Clarithromycin</td>
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<td>0.06 0.12 4</td>
</tr>
<tr>
<td>U. urealyticum (doxycycline resistant) (15)</td>
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<tr>
<td>BAY 12-8039</td>
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<td>Sparfloxacin</td>
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<tr>
<td>Doxycycline</td>
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<td>16 32 ND</td>
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<td>Clarithromycin</td>
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<td>0.06 0.12 4</td>
</tr>
</tbody>
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a 50% and 90%, MICs at which 50 and 90% of the isolates, respectively, are inhibited.
b ND, not determined.
days for *M. pneumoniae*, and at 7 days for *M. genitalium*. For *U. urealyticum*, the MICs were determined by a broth dilution method performed in microtiter plates. Shepard liquid medium (2) containing antibiotic dilutions (0.015 to 32 μg/ml) was inoculated with *U. urealyticum* to yield approximately $5 \times 10^3$ to $5 \times 10^4$ color-changing units in 0.2 ml and incubated at 37°C. The final MIC was the lowest antibiotic concentration without color change that remained stable after 40 h of incubation.

Table 1 compares the in vitro activities of BAY 12-8039 and the other antimicrobials. The overall activity of BAY 12-8039 was very good against all the mycoplasmas tested. A concentration of BAY 12-8039 of 0.5 μg/ml inhibited all the strains, except the fluoroquinolone-resistant mutants of *M. hominis* PG21.

For *M. pneumoniae* and *M. genitalium*, the MICs of BAY 12-8039 were comparable to those of sparfloxacin, doxycycline, and clarithromycin. The MICs of BAY 12-8039 and sparfloxacin for *M. hominis* and *M. fermentans* were similar, showing the good activities of these fluoroquinolones. As expected, *M. hominis* and *M. fermentans* were resistant to clarithromycin. Against *M. penetrans*, BAY 12-8039 was fourfold more active than clarithromycin but two- to fourfold less active than sparfloxacin. Furthermore, the activity of BAY 12-8039 was compared with that of sparfloxacin against the eight multistep fluoroquinolone-resistant mutants of the reference strain *M. hominis* PG21. A comparable increased resistance to both antibiotics was found (MIC of BAY 12-8039, 1 to 8 μg/ml; MIC of sparfloxacin, 0.06 to 4 μg/ml).

BAY 12-8039 was very active against all the ureaplasma strains studied. Doxycycline-resistant strains were as susceptible as doxycycline-susceptible strains to BAY 12-8039 and sparfloxacin, as previously described for other fluoroquinolones (5–7).

The minimal bactericidal concentrations (MBCs) of BAY 12-8039 and of the comparative compounds were determined for a reference strain of each species in test tubes containing 2 ml of Shepard broth medium for *U. urealyticum* or 2 ml of Hayflick modified broth medium for the other mycoplasma species. When the MIC was recorded, 100-μl aliquots were transferred from tubes without color change to 5 ml of fresh antibiotic-free broth. The MBC was the lowest antibiotic concentration inhibiting a color change in this culture within 4 to 10 days, according to the species.

For all mycoplasma species (Table 1), the MBCs of BAY 12-8039 were two- to eightfold higher than the MICs. Similar results were observed with BAY 12-8039, sparfloxacin, and clarithromycin for *M. pneumoniae* and *M. genitalium*. For *M. hominis* and *M. fermentans*, the MBCs of BAY 12-8039 and sparfloxacin were identical. Doxycycline exhibited higher values. For *U. urealyticum* doxycycline-susceptible strains, the MBC of BAY 12-8039 was identical to that of sparfloxacin and lower than those of doxycycline and clarithromycin. For *U. urealyticum* doxycycline-resistant strains, BAY 12-8039 showed the lowest MBC. These results indicate that both fluoroquinolones were bactericidal in vitro against all mycoplasma species examined.

To summarize, BAY 12-8039, like sparfloxacin (4, 8), ranked among the best fluoroquinolones active against mycoplasmas. Furthermore, this antibiotic was bactericidal for all mycoplasma strains tested. These data suggest that BAY 12-8039 may be useful for the treatment of respiratory or genital infections in which mycoplasmas are involved.

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