Activities of a New Fluoroketolide, HMR 3787, and Its (Des)-Fluor Derivative RU 64399 Compared to Those of Telithromycin, Erythromycin A, Azithromycin, Clarithromycin, and Clindamycin against Macrolide-Susceptible or -Resistant Streptococcus pneumoniae and S. pyogenes

KENSUKE NAGAI,1 TODD A. DAVIES,1 LOIS M. EDNIE,1 ANDRE BRYSKIER,2 ELIZABETH PALAVECINO,3 MICHAEL R. JACOBS,3 AND PETER C. APPELBAUM1

Hershey Medical Center, Hershey, Pennsylvania 170331; Hoechst Marion Roussel Aventis Anti-infectives, Romainville, France2; and Case Western Reserve University, Cleveland, Ohio 441063

Received 1 March 2001/Returned for modification 1 June 2001/Accepted 30 July 2001

Macrolide resistance in Streptococcus pneumoniae has been encountered in many countries and is usually mediated by one of two mechanisms: activity of ribosomal methylases encoded by ermB genes and rarely ermA (ermTR), which results in strains being highly resistant to all macrolides, azalides, and clindamycin, and drug efflux encoded by mef genes, which confers lower-level resistance to 14-membered macrolides and azalides but does not affect the response to 16-membered macrolides or clindamycin (2, 3, 21, 22).

In many European countries, such as France, Spain, and Italy, where a high prevalence of macrolide resistance is encountered, ermB mediates the predominant macrolide resistance mechanism for S. pneumoniae, although mefE is also found (2, 21). Other mechanisms of macrolide resistance have been described for S. pneumoniae, including mutations in L4 and L22 and mutations in 23S rRNA at position 2058 or 2611 (Escherichia coli numbering system) (23, 24). Telithromycin has proved to be very active against most pneumococci, including strains with macrolide resistance mechanisms listed above (9, 11, 14, 18).

In recent years, macrolide resistance has also been increasingly detected in Streptococcus pyogenes in Europe and other areas of the world and is mediated by ermA, mefA, and less commonly ermB mechanisms (1, 4, 6–8, 10, 12, 13, 15, 16, 17, 19, 20, 25–27). Telithromycin has been reported to be active against S. pyogenes with inducible ermA- and mefA-mediated resistance, but it has lower activity against strains with the constitutive ermB resistance mechanism (5).

HMR 3787 (Fig. 1) is a new fluoroketolide with a broad antibacterial spectrum covering gram-positive bacteria, fastidious gram-negative bacilli and intracellular and atypical organisms (H. Drugeon, A. Bryskier, and P. Bemer-Melchior, Abstr. 40th Intersci. Conf. Antimicrob. Agents Chemother., abstr. 1818, 2000). The present study examines the susceptibilities of a collection of macrolide-susceptible and macrolide-resistant S. pneumoniae and S. pyogenes isolates, with different macrolide resistance mechanisms, to a new fluoroketolide, HMR 3787, and its (des)-fluor derivative, RU 64399 (Fig. 1), in comparison with susceptibilities to telithromycin, erythromycin A, azithromycin, clarithromycin, and clindamycin.

For S. pneumoniae, 41 macrolide-susceptible isolates and 134 isolates with macrolide resistance mechanisms mediated by ribosomal methylase, efflux, ribosomal protein mutations, or 23S rRNA mutations were tested. For S. pyogenes, 41 macrolide-susceptible strains and 80 resistant strains were tested (Table 1). Cultures were from our collection except for macrolide-resistant S. pyogenes isolates, many of which were isolated within the past 4 years in Chile. HMR 3787, RU 64399, and telithromycin were obtained from Aventis Hoechst Marion Roussel Anti-infectives, Paris, France, and other compounds were obtained from their respective manufacturers. Agar dilution MIC methodology, using sheep blood Mueller-Hinton

FIG. 1. Chemical structures of HMR 3787 and RU 64399.
TABLE 1. MICs of compounds against *S. pneumoniae* and *S. pyogenes* isolates with erythromycin A susceptibility or known resistance mechanisms

<table>
<thead>
<tr>
<th>Compound and microorganism</th>
<th>MIC (μg/ml) for isolates with characteristic</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Erythromycin A susceptible</td>
</tr>
<tr>
<td></td>
<td>S. pneumoniae</td>
</tr>
<tr>
<td>Penicillin G</td>
<td>0.016–4.0</td>
</tr>
<tr>
<td>Erythromycin A</td>
<td>0.008–0.06</td>
</tr>
<tr>
<td>Azithromycin</td>
<td>0.03–0.125</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>0.008–0.06</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>0.016–0.06</td>
</tr>
<tr>
<td>Telithromycin</td>
<td>0.004–0.06</td>
</tr>
<tr>
<td>RU 64399</td>
<td>0.004–0.016</td>
</tr>
<tr>
<td>HMR 3787</td>
<td>0.004–0.016</td>
</tr>
</tbody>
</table>

*amefE for *S. pneumoniae* and *mefA* for *S. pyogenes*. For number of strains tested, see the text.
aggar plates incubated in air for 24 h and using recommended quality control strains with each run, were used (9, 11). Macrolide resistance mechanisms were determined by PCR for erm and mef in both species as previously described (21). For 23S rRNA methylase genes, the encoding genes encoding L4 and L22 were amplified by PCR and sequenced (3, 21, 23, 24). MICs of drugs tested against both species are shown in Table 1. All agents were highly active against macrolide-susceptible S. pneumoniae isolates for which MICs at which 50% of the bacteria were inhibited (MIC<sub>50</sub>) of macrolides and clindamycin were 0.03 to 0.06 μg/ml and MIC<sub>50</sub> were 0.03 to 0.125 μg/ml. MIC<sub>50</sub> and MIC<sub>90</sub> for the three ketolides tested were 0.008 and 0.016 μg/ml, respectively. Overall, HMR 3787 and telithromycin were the most active compounds tested against pneumococci, irrespective of the macrolide resistance mechanism, with MIC<sub>50</sub> and MIC<sub>90</sub> similar to those of S. pneumoniae (Table 1). All macrolide-resistant strains showed high-level resistance to macrolides, whereas all mefA strains and some ermA strains were susceptible to clindamycin. Telithromycin and HMR 3787 were equally active against strains carrying mefA and ermA genes, with MIC<sub>50</sub> and MIC<sub>90</sub> of 0.016 to 0.05 and 0.03 to 0.5, respectively. However, HMR 3787 was more active than the other ketolides against strains with ermB, with MIC<sub>50</sub> and MIC<sub>90</sub> of 2.0 and 4.0 μg/ml, compared to 16.0 and >16.0 μg/ml for telithromycin and >16.0 and >16.0 μg/ml for RU 64399.

Our study demonstrates that HMR 3787 is as active as telithromycin (9, 11, 14, 18) and RU 64399 against macrolide-susceptible pneumococci and slightly more active than RU 64399 against macrolide-resistant pneumococci. HMR 3787 is also two to fourfold more active than telithromycin and RU 64399 against ermB S. pyogenes, while being as active as telithromycin against erythromycin-susceptible, ermA and mefA S. pyogenes strains. Although HMR 3787 MICs for ermB S. pyogenes strains were higher than those for ermA and mefA strains, they were lower (MIC<sub>50</sub> and MIC<sub>90</sub> 2.0 and 4.0 μg/ml, respectively) than those of telithromycin and RU 64399 (16 and >16.0 for telithromycin; >16.0 and >16.0 μg/ml for RU 64399). In a recent paper, Bemer-Melchior and colleagues (5) have reported erythromycin, azithromycin, clarithromycin, clindamycin, and telithromycin MICs against ermB, ermA, and mefA S. pyogenes which were similar to those reported in the present study. The reason why telithromycin is active against ermB pneumococci, but not against ermB S. pyogenes, is not known at present.

All three ketolides were very active (MIC<sub>50</sub> ≤0.5 μg/ml) against pneumococci with L4 and L22 proteins and 23S rRNA mutations. Most L4 strains appear by MIC testing to have a pattern similar to that of mef strains, being clindamycin susceptible and with macrolide MICs of 1.0 to 16.0 μg/ml. However, for some strains, macrolide MICs are higher (>32.0 μg/ml).

HMR 3787 represents an expanded-spectrum ketolide, with activity against macrolide-resistant streptococcis similar to telithromycin’s except for lower MICs against ermB isolates in S. pyogenes. By contrast, RU 64399 has a level of activity slightly lower than telithromycin’s against macrolide-resistant pneumococci and similar to telithromycin’s against ermB S. pyogenes.

This study was supported by a grant from Aventis Hoechst-Marion Roussel Anti-infectives, Romainville, France.

REFERENCES


