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Comparative Activities of Telithromycin (HMR 3647), Levofloxacin, and Other Antimicrobial Agents against Human Mycoplasmas

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The activities of telithromycin and levofloxacin against 99 mycoplasma strains were compared to those of several macrolides, ofloxacin, and doxycycline. Telithromycin MICs of ≤0.25 μg/ml were found for all isolates, except for *Mycoplasma hominis*, while levofloxacin was active at concentrations of ≤1 μg/ml against all species studied.

Only a few classes of antimicrobial agents are available for the treatment of mycoplasmal infections in humans. They are mainly the tetracyclines, macrolides, and fluoroquinolones (15). Resistance to tetracyclines by the acquisition of the *tetM* gene has been frequently described for urogenital mycoplasmas (12, 13). Concerning macrolides, *Mycoplasma hominis* and *Mycoplasma fermentans* are innately resistant to erythromycin but not to josamycin, while *Mycoplasma pneumoniae* and *Mycoplasma genitalium* are very susceptible to all these antibiotics. The newest macrolides are semisynthetic compounds known as ketolides (6). They have improved activity against microorganisms resistant to macrolides, especially gram-positive bacteria (8). One of them is telithromycin (HMR 3647), an erythromycin A derivative. Newer fluoroquinolones with enhanced activity against gram-positive bacteria and intracellular organisms have been developed (9). Levofloxacin, the *l*-isomer of ofloxacin, is one of these (10, 14).

In this study, we compared the in vitro activity of telithromycin to those of several macrolides, including erythromycin A, roxithromycin, dirithromycin, clarithromycin, azithromycin, josamycin, and spiramycin, and the in vitro activity of levofloxacin to that of ofloxacin against clinical and reference strains of different human mycoplasma species. Doxycycline was used as a reference compound. Each of the following antimicrobial agents was provided by the manufacturer: telithromycin, levofloxacin, erythromycin A, roxithromycin, and ofloxacin (Hoechst Marion Roussel, Romainville, France); azithromycin and doxycycline (Pfizer, Orsay, France); clarithromycin (Abbott, Rungis, France); dirithromycin (Lilly France, Saint Cloud, France); and josamycin and spiramycin (Rhône-Poulenc-Rorer, Vitry-sur-Seine, France).

Ninety-nine strains, including 25 strains of *M. pneumoniae* (24 clinical respiratory isolates and 1 reference strain [FH]), 5 strains of *M. genitalium* (4 clinical isolates and 1 reference strain [G37]), 32 strains of *M. hominis* (29 josamycin-susceptible clinical isolates, 2 josamycin-resistant clinical isolates, and 1 reference strain [PG21]), 5 strains of *M. fermentans* (4 clinical isolates and 1 reference strain [PG18]), 2 strains of *Mycoplasma penetrans* (1 urethral isolate and 1 reference strain [GTU-54]), 15 *Ureaplasma urealyticum* doxycycline-susceptible strains (14 clinical isolates and 1 reference strain, serotype 8), and 15 *U. urealyticum* doxycycline-resistant strains (14 clinical isolates and 1 reference strain, serotype 9), were studied.

Susceptibility testing was carried out as previously described (1) by an agar dilution method with Hayflick modified agar for mycoplasmal strains and by a broth dilution method with Shepard medium for ureaplasmal strains. Minimal bactericidal concentrations (MBCs) of the different compounds were determined as previously reported (3) for a reference strain of each species.

The in vitro activities of telithromycin, levofloxacin, and other antimicrobial agents are shown in Table 1. Telithromycin inhibited all mycoplasmal and ureaplasmal strains, except for *M. hominis*, at ≤0.25 μg/ml. Telithromycin shared the best activity (MIC at which 90% of strains were inhibited [MIC_{90}] or MIC range, ≤0.015 μg/ml) with erythromycin A, roxithromycin, clarithromycin, and azithromycin against *M. pneumoniae* isolates and with erythromycin A and roxithromycin against *M. genitalium* isolates. Telithromycin had the lowest MIC range, from 0.06 to 0.25 μg/ml, against both *M. fermentans* and *M. penetrans*. Against *M. hominis* isolates for which josamycin was the only active macrolide, telithromycin had a high MIC_{90} (16 μg/ml), but this MIC_{90} was fourfold lower than those of the macrolides, except for josamycin. However, the two josamycin-resistant clinical isolates of *M. hominis* previously described (5) were found to be as resistant to telithromycin as to the macrolides (MIC, >128 μg/ml).

Against *U. urealyticum* strains, telithromycin was found to be as active as clarithromycin, the most active macrolide tested, with an MIC_{90} of 0.03 μg/ml. Furthermore, ketolide activity was the same whatever the doxycycline susceptibility profile of the ureaplasmal isolates. Our study on telithromycin globally confirms our results previously reported for other ketolides, such as RU 004, RU 306, RU 469, and RU 399, for mycoplasmas, with MICs ranking in similar ranges (2).

The MBCs of telithromycin were found to be close to the MICs for *M. pneumoniae* and *M. genitalium* (MBCs, ≤0.12 μg/ml), as were the MBCs of the macrolides tested. Against *M. fermentans* and *M. penetrans*, the telithromycin MBCs were found to be 2 and 1 μg/ml, respectively, much lower than those of the macrolides, especially for *M. fermentans* (MBCs of comparative macrolides, 16 to >128 μg/ml). Against *M. hominis*, the telithromycin MBC (16 μg/ml) was comparable to that of josamycin, the only macrolide that had low MICs against this species. Against *U. urealyticum*, despite a very low MIC_{90}, telithromycin did not have good bactericidal activity, with an MBC of ≥32 μg/ml. Only two macrolides, clarithromycin and

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TABLE 1. Comparative in vitro activities of telithromycin, levofloxacin, and other antimicrobial agents against human mycoplasmas

Organism (no. of strains tested) and antimicrobial agent	MIC (μg/ml)		
	Range	50%	90%
M. pneumoniae (25)			
Telithromycin	≤0.015	≤0.015	≤0.015
Erythromycin A	≤0.015	≤0.015	≤0.015
Roxithromycin	≤0.015–0.03	≤0.015	≤0.015
Dirithromycin	≤0.015–0.06	≤0.015	0.06
Clarithromycin	≤0.015	≤0.015	≤0.015
Azithromycin	≤0.015	≤0.015	≤0.015
Josamycin	≤0.015–0.03	≤0.015	0.03
Spiramycin	≤0.015–0.25	0.06	0.25
Levofloxacin	0.5–1	0.5	1
Ofloxacin	1	1	1
Doxycycline	0.06–0.25	0.12	0.25
M. genitalium (5)			
Telithromycin	≤0.015	—[a]	—
Erythromycin A	≤0.015	—	—
Roxithromycin	≤0.015	—	—
Dirithromycin	≤0.015–0.12	—	—
Clarithromycin	≤0.015–0.06	—	—
Azithromycin	≤0.015–0.03	—	—
Josamycin	0.015–0.03	—	—
Spiramycin	0.12–1	—	—
Levofloxacin	0.5–1	—	—
Ofloxacin	1	—	—
Doxycycline	0.06–0.12	—	—
M. hominis (30)[b]			
Telithromycin	2–16	16	16
Erythromycin A	>64	>64	>64
Roxithromycin	>64	>64	>64
Dirithromycin	>64	>64	>64
Clarithromycin	>64	>64	>64
Azithromycin	32–>64	64	>64
Josamycin	0.06–0.25	0.25	0.25
Spiramycin	32–>64	>64	>64
Levofloxacin	0.12–0.5	0.25	0.25
Ofloxacin	0.25–1	0.25	0.5
Doxycycline	0.03–16	0.06	16
M. fermentans (5)			
Telithromycin	0.06–0.25	—	—
Erythromycin A	64–>64	—	—
Roxithromycin	32–64	—	—
Dirithromycin	64–>64	—	—
Clarithromycin	16–32	—	—
Azithromycin	2–8	—	—
Josamycin	0.12–0.5	—	—
Spiramycin	2–4	—	—
Levofloxacin	0.06	—	—
Ofloxacin	0.12	—	—
Doxycycline	0.06	—	—
M. penetrans (2)			
Telithromycin	0.12	—	—
Erythromycin A	2	—	—
Roxithromycin	0.5	—	—
Dirithromycin	16	—	—
Clarithromycin	0.12	—	—
Azithromycin	0.12–0.5	—	—
Josamycin	0.12–0.25	—	—
Spiramycin	16	—	—
Levofloxacin	0.06	—	—
Ofloxacin	0.12	—	—
Doxycycline	0.12–0.25	—	—
U. urealyticum (doxycycline susceptible) (15)			
Telithromycin	≤0.015–0.06	0.03	0.03
Erythromycin A	0.12–1	0.25	0.5
Roxithromycin	0.06–0.5	0.25	0.25
Dirithromycin	0.25–2	1	2
Clarithromycin	≤0.015–0.03	0.03	0.03
Azithromycin	0.06–0.25	0.25	0.25
Josamycin	0.03–0.12	0.06	0.12
Spiramycin	4–32	16	32
Levofloxacin	0.5–1	0.5	0.5
Ofloxacin	1–2	1	2
Doxycycline	0.06–0.5	0.12	0.25
U. urealyticum (doxycycline resistant) (15)			
Telithromycin	≤0.015–0.06	0.03	0.06
Erythromycin A	0.12–1	0.5	1
Roxithromycin	0.06–0.5	0.25	0.25
Dirithromycin	0.25–8	1	2
Clarithromycin	≤0.015–0.06	0.03	0.03
Azithromycin	0.12–0.5	0.25	0.25
Josamycin	0.03–0.12	0.12	0.12
Spiramycin	8–32	32	32
Levofloxacin	0.5–1	1	1
Ofloxacin	1–2	1	2
Doxycycline	16–32	32	32

[a] —, not determined.
[b] The two josamycin-resistant isolates are not included.

azithromycin, had lower MBCs, between 1 and 8 μg/ml. In summary, except against *M. hominis* and *U. urealyticum*, telithromycin was bactericidal against mycoplasmal isolates.

Comparative results for levofloxacin are also shown in Table 1. All the mycoplasma strains studied were inhibited by 1 μg of levofloxacin per ml. Against the five mycoplasma species studied, levofloxacin had activity similar to that of ofloxacin, with equal MICs for *M. pneumoniae* and *M. genitalium* (MIC range, 0.5 to 1 μg/ml) or an MIC twofold lower for *M. hominis*, *M. fermentans*, and *M. penetrans*. Against *U. urealyticum*, levofloxacin was two- to fourfold more active than ofloxacin (MIC_{90}, 0.5 to 1 μg/ml), with similar activity against doxycycline-susceptible or -resistant strains. In a previous study, Ullmann et al. (16) obtained results within the same range as ours for levofloxacin against *U. urealyticum* but not against *M. hominis*, for which they found an MIC_{90} fourfold higher. Waites et al. (17) found the same MIC_{90} of levofloxacin as we did against *M. hominis* by the E test method (17). It should be noted that levofloxacin showed only slightly enhanced activity against mycoplasmas in comparison to ofloxacin, with MICs only one dilution higher. In terms of in vitro activity, levofloxacin does not seem to be significantly more active than its *l*-isomer, ofloxacin, against mycoplasmas.

For all mycoplasmal and ureaplasmal strains, MBCs of levofloxacin were equal to or twofold lower than those of ofloxacin, ranging from 0.12 μg/ml against *M. penetrans* to 4 μg/ml against *M. genitalium* and *M. hominis*. For *M. pneumoniae*, *M. genitalium*, *M. penetrans*, and *U. urealyticum*, MBCs were only 2- to 4-fold higher than MICs, while they were 8- to 16-fold higher than MICs for *M. hominis* and *M. fermentans.* However,

levofloxacin seemed to be bactericidal in vitro against mycoplasmas, with MBCs of ≤4 μg/ml.

As a reference compound, doxycycline showed good activity, ranging between those of telithromycin and levofloxacin, against mycoplasmas and *U. urealyticum* doxycycline-susceptible strains (MICs, 0.03 to 0.25 μg/ml), except for *M. hominis* strains, some of which were doxycycline resistant.

In conclusion, our data suggest that levofloxacin, like other new fluoroquinolones (3, 4, 7, 11, 16), may be interesting for the treatment of respiratory and urogenital mycoplasma infections. Telithromycin, belonging to the new class, ketolides, seems to be very effective against mycoplasmas, except for *M. hominis*, and could have useful clinical activity against these microorganisms.

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