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In Vitro Activities of Tigecycline (GAR-936) against Multidrug-Resistant *Staphylococcus aureus* and *Streptococcus pneumoniae*

During recent years, a dramatic increase in bacterial resistance to antibiotics has been observed worldwide, both in community and nosocomial isolates, curtailing the use of many valuable antibiotics. In France, more than 50% of *Streptococcus pneumoniae* strains isolated in the community are resistant to penicillin and macrolides (8), and more than 40% of *Staphylococcus aureus* strains isolated in hospitals are resistant to β-lactams, aminoglycosides, macrolides, and fluoroquinolones, including the newer compounds (≈100% of the methicillin-resistant *S. aureus* [MRSA] strains) (5). *S. aureus* strains with low-level resistance to glycopeptides have been isolated in our hospital for more than 10 years (6), and resistance to quinupristin-dalfopristin (Synercid) is not uncommon due to the frequent use of oral pristinamycin in France. Most of these multidrug-resistant (MDR) bacteria are resistant to tetracyclines, emphasizing the need for new compounds.

Tigecycline (GAR-936) is the 9-*t*-butylglycylamino derivative of minocycline, a new generation of tetracyclines called glycylcyclines. These glycylcyclines overcome tetracycline resistance due to both ribosomal protection and efflux determinants (1–3, 7). The aim of this study was to assess the in vitro activity of GAR-936 against MDR *S. pneumoniae* and *S. aureus* in comparison with tetracycline, minocycline, telithromycin, linezolid, and quinupristin-dalfopristin.

Bacterial strains. A total of 133 *S. aureus* and 105 *S. pneumoniae* epidemiologically unrelated strains were selected for MIC studies.

Among the 133 *S. aureus* strains, 38 were tetracycline susceptible (15 methicillin-susceptible *S. aureus* [MSSA] and 23 MRSA strains) and 95 were tetracycline resistant (28 MSSA and 67 MRSA strains); quinupristin-dalfopristin resistance was observed in 25 strains (6 MSSA and 19 MRSA), and 11 strains (all MRSA) were considered as glycopeptide-intermediate *S. aureus* strains.

Among the 105 *S. pneumoniae* strains, 13 strains were tetracycline susceptible (6 penicillin-resistant strains), and 92 strains were resistant to tetracycline (74 penicillin-resistant strains).

Antibiotics. Standard reference powders were obtained from Wyeth Ayerst (tigecycline [GAR-936] and minocycline), Pharmacia (linezolid), and Aventis (telithromycin, quinupristin-dalfopristin, and tetracycline).

MICs. Bacterial strains were grown overnight in brain heart infusion (BHI) broth (*S. aureus*) or a combination of BHI broth and 10% horse serum (*S. pneumoniae*) and diluted in order to obtain 10^6 CFU/ml. A twofold dilution of the antibiotics was done in Mueller-Hinton agar (MHA; for *S. aureus* strains) or a combination of MHA and 5% horse blood (for *S. pneumoniae* strains). Bacteria were deposited with a Steers replication device in order to obtain ≈10^3 to 10^4 CFU/spot. All the plates were incubated for 18 h at 37° in ambient air. The MIC was considered as the lowest concentration inhibiting visible growth (or <3 colonies). Strains were classified as susceptible, intermediate, or resistant according to NCCLS criteria.

The activity of GAR-936 and other antibiotics on *S. aureus* is presented in Table 1 delineating the most remarkable resistance patterns: resistance to tetracycline, β-lactams, and quinupristin-dalfopristin. Against tetracycline-susceptible strains, the mode MIC of GAR-936 was equal to the MICs of tetracycline, quinupristin-dalfopristin, and telithromycin, lower than the MIC of linezolid, but 1 dilution higher than that of minocycline. Against tetracycline-resistant strains, GAR-936 was by far the most active compound, with a mode MIC of 0.5 μg/ml in contrast to a mode MIC of 4 to 128 μg/ml for other antibiotics. Moreover, there was no shift to higher GAR-936 MICs for strains resistant to tetracycline and minocycline or other antibiotics, as inferred from the very narrow MIC range (mode ± 1 dilution) despite the diversity of strains and resistance mechanisms (minocycline MICs ranged from 0.12 to 16 μg/ml). This absence of increased resistance to GAR-936–in other words, the absence of both cross-resistance and associated resistance–was unexpected since resistant mutants can be selected in vitro.

The activity against *S. pneumoniae* is presented in Table 1. Against tetracycline-susceptible strains, as noted also for tetracycline-susceptible *S. aureus* strains, the mode MIC of GAR-936 was 1 dilution lower than that of tetracycline and 1 dilution

TABLE 1. MICs of GAR-936 and other drugs for *S. aureus* and *S. pneumoniae* strains

Organism	Total no. of strains	MIC[a] (μg/ml)					
		GAR-936	TET	MIN	LIN	TEL	SYN
S. aureus strains							
Tetracycline susceptible	38	0.25–1 (0.5)	0.5–4 (0.5)	0.12–0.5 (0.25)	1–4 (2)	0.12–128 (0.5)	0.5–16 (0.5)
Tetracycline resistant	84	0.25–1 (0.5)	16–128 (64)	0.12–16 (4)	0.25–4 (2)	0.12–128 (128)	0.25–32 (1)
Glycopeptide intermediate	11	0.5–1 (0.5)	32–64 (32)	2–8 (4)	1–2 (2)	>128	0.5–16 (1)
S. pneumoniae strains							
Tetracycline susceptible	13	0.12–0.5 (0.25)	0.25–2 (0.5)	0.12–0.5 (0.12)	0.5–2 (1)	0.01–1 (0.03)	1–2 (2)
Tetracycline resistant	92	0.06–0.5 (0.12)	8–128 (64)	1–64 (8)	0.5–2 (1)	0.03–2 (0.06)	0.5–4 (1)

[a] Values are the MIC ranges of the drugs for the strains; the MICs at which 50% of the strains are inhibited are given in parentheses. TET, tetracycline; MIN, minocycline; LIN, linezolid; TEL, telithromycin; SYN, quinupristin-dalfopristin.

higher than that of minocycline. Against tetracycline-resistant *S. pneumoniae* strains, GAR-936 was 32- to 64-fold more active than minocycline, with no GAR-936 MIC exceeding 0.5 μg/ml versus a minocycline MIC of 64 μg/ml. Against penicillin-resistant strains, the MICs of GAR-936 were lower by 1 dilution than the MICs for penicillin susceptible strains.

This interesting finding, not previously reported, must be confirmed in isogenic strains, however. As with *S. aureus* strains, no shift in the MICs of GAR-936 have been observed for strains resistant to other antibiotics, particularly macrolides and fluoroquinolones. This result suggests that the risk of selection by unrelated antibiotics of multidrug-resistant strains, as frequently occurs with *S. aureus* and *S. pneumoniae* strains (4), is minimized.

These data indicate that GAR-936 is a very valuable compound and warrants further in vitro and clinical studies.

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