Antibacterial activities of vancomycin, teicoplanin, daptomycin, and RP 59500, a new streptogramin antibiotics, against methicillin-susceptible and methicillin-resistant *Staphylococcus aureus*

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The antibacterial activities of vancomycin, teicoplanin, daptomycin, and RP 59500 against 395 *Staphylococcus aureus* strains isolated in various hospitals throughout Japan from 1987—1989 were determined. These agents showed potent activity, and no strains were resistant to these agents. All strains tested were inhibited by vancomycin, teicoplanin, daptomycin, and RP 59500 at 3.13, 1.56, 0.78, and 3.13 μg/ml, respectively. The susceptibilities distribution of these four agents against methicillin-resistant *S. aureus* were almost unchanged compared them against methicillin-susceptible *S. aureus*.

Key words: vancomycin, teicoplanin, daptomycin, RP 59500, MRSA

The emergence of methicillin-resistant *Staphylococcus aureus* (MRSA) and their nosocomial infections have become a serious problem in hospitals. MRSA have become resistant to β-lactams, fluoroquinolones, aminoglycosides, and macrolides in addition to methicillin. These multiple resistance in especially high-MRSA has caused serious difficulty in the treatment with chemotherapeutic agents[1~3]. However, It has been reported that vancomycin, teicoplanin, daptomycin, and RP 59500 have potent activity against *S. aureus* including multiply resistant MRSA. We investigated the *in vitro* activity of vancomycin, teicoplanin, daptomycin, and RP 59500 against 395 *S. aureus* strains isolated in various hospitals throughout Japan from 1987—1989.

The antimicrobial agents used in this study were vancomycin (Shionogi Seiyaku Co.)[4~6], teicoplanin (Merrell Dow Co.)[7~10], daptomycin (Eli Lilly Co.)[11], RP 59500 (Rhone Poulenc Co.)[12], and oxacillin (Banyu Seiyaku Co.). The tested *S. aureus* were isolated clinically in various hospitals throughout in Japan from 1987 to 1989. The MIC was determined by two-fold serial agar dilution method with Sensitivity Disk Agar-N (Nissui Pharmaceutical Co., Ltd., Tokyo). An inoculum of about 10^4 CFU per spot was applied to the agar surface containing various concentrations of agents with an inoculation apparatus (Microplanter; Sakuma Seisakusho, Tokyo). The MIC was defined as the lowest concentration of agent at which visible bacterial growth was inhibited after incubation for 24 h at 35°C.

The antibacterial activities of vancomycin, teicoplanin, daptomycin, and RP 59500 were compared between methicillin-susceptible *S. aureus* (MIC of

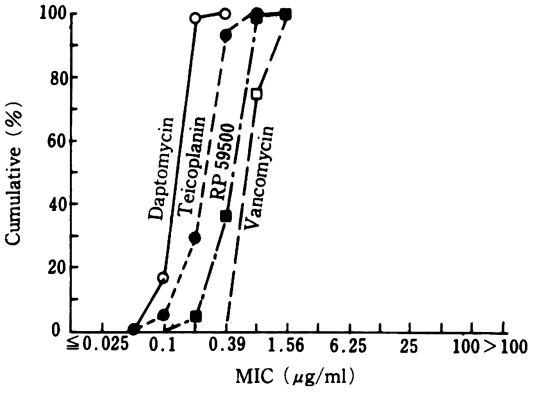

Fig. 1. Antibacterial activity against 119 strains of methicillin-susceptible *Staphylococcus aureus*.

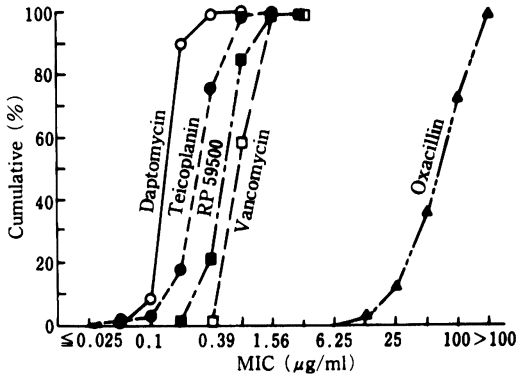

Fig. 2. Antibacterial activity against 276 strains of methicillin-resistant *Staphylococcus aureus*.

oxacillin, ≤3.13 μg/ml) and MRSA (MIC of oxacillin, ≥6.25 μg/ml) isolates. As shown in Figs. 1 and 2, these four agents showed high antibacterial activities against all strains tested including MRSA strains. The MICs of vancomycin, teicoplanin, daptomycin, and RP 59500 for 90% against MSSA and MRSA strains were 1.56, 0.39, 0.20, and 0.78 μg/ml and 1.56, 0.78, 0.20, and 1.56 μg/ml, respectively. It has been reported that the isolation frequency of MRSA strains resistant to not only β-lactams but also to fluoroquinolones, macrolides, aminoglycosides, and tetracyclines was significantly higher than the corresponding values for MSSA[1]. However, the susceptibilities distribution of these four antibiotics against MSSA isolates were almost unchanged compared them against MRSA isolates. All strains tested were inhibited by vancomycin, teicoplanin, daptomycin, and RP 59500 at 3.13, 1.56, 0.78, and 3.13 μg/ml, respectively. The activity of ofloxacin and minocycline against MRSA isolates from 1985 was strong, and high resistant isolates to them did not observe. But against MRSA isolates from 1987−1989, high resistant isolates to them appeared (data not shown). It should be noted that there were no strains resistant to vancomycin, teicoplanin, daptomycin, and RP 59500 against all strains tested, even among the MRSA strains. These results were similar to other reports.

It has been reported that vancomycin was effective against infections caused by MRSA[13]. The strong potency of antibacterial activity of teicoplanin, daptomycin, and RP 59500 suggest that these antibiotics are useful for MRSA infection.

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Literature Cited

1) Muratani T, Watanabe M, Yoshida M, Mitsuhashi S: Isolation frequencies of strains resistant to 16 antimicrobial agents among methicillin-susceptible and low- and high-methicillin resistant *Staphylococcus aureus*. Chemotherapy 39: 1148～1151, 1991
2) Goto H, Goto M, Oka S, Shimada K, Shimizu K, Goto S, Ueno K, Hara K: The prevalence of multiply resistant *Staphylococcus aureus* in Japan during 1986 and 1988. Chemotherapy 37: 1334～1341, 1989
3) Gravenkemper C F, Brodie J L, Kirby W M M: Resistance of coagulase-positive staphylococci to methicillin and oxacillin. J Bacteriol 89: 1005～1010, 1965
4) Nagarajan R: Antibacterial activities and modes of action of vancomycin and related glycopeptides. Antimicrob Agents Chemother 35: 605～609, 1991
5) Jordan D C, Inniss W E: Selective inhibition of ribonucleic acid synthesis in *Staphylococcus aureus* by vancomycin. Nature 184: 1894～1895, 1959
6) Jordan D C, Mallory H D C: Site of action of vancomycin on *Staphylococcus aureus*. Antimicrob Agent Chemother: 489～494, 1965
7) Greenwood D: Microbiological properties of teicoplanin. J Antimicrob Chemother 21: suppl. A, 1～13, 1988
8) Laethem Y V, Hermans P, Wit S D, Goosens H, Clumerck N: Teicoplanin compared with vancomycin in methicilin-resistant *Staphylococcus aureus* infections: preliminary results. J Antimicrob Chemother 21, suppl. A, 81～87, 1988
9) Smith S: In vitro comparison of A-56619, A-56620, amifloxacin, ciprofloxacin, enoxacin norfloxacin, and ofloxacin against methicillin-resistant *Staphylococcus aureus*. Antimicrob Agents Chemother 29: 325～326, 1986
10) Mitsuhashi S, Nakanishi N, Inoue K: Antibacterial activity of teicoplanin against gram-positive bacteria isolated in Japan. Episome Rep Med Sci 6: 6～8, 1991
11) Fass R J, Helsel V L: In vitro activity of LY 146032 against staphylococci, streptococci, and enterococci. Antimicrob Agents Chemother 30: 781～784, 1986

12) Inoue M, Okamoto R, Inoue K, Mitsuhashi S: Comparison of the in vitro antibacterial activities of RP 59500 against clinical isolates of bacteria. J Antimicrob Chemother: in press

13) Shimada, K, Hanatani Y, Meguro H, Kanno H: Intravenous vancomycin in the treatment of severe MRSA infections. Chemotherapy 40: 86～101, 1992

Vancomycin, teicoplanin, daptomycin および RP 59500 のメチシリン感受性およびメチシリン耐性黄色ブドウ球菌に対する抗菌活性

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我々は1987～1989年に日本各地の病院などで分離された *Staphylococcus aureus* 395株に対する vancomycin, teicoplanin, daptomycin および RP 59500 の抗菌活性を調べた。その結果，上記4薬剤とも強い抗菌活性を示した。vancomycin teicoplanin, daptomycin および RP 59500 はそれぞれ 3.13, 1.56, 0.78 および 3.13 μg/ml ですべての菌株の発育を阻害した。これら4薬剤の methicillin-resistant *S. aureus* に対する感受性分布は methicillin-susceptible *S. aureus* に対するそれとほとんど同様のパターンを示した。

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