Clinical efficacy and safety in patients treated with teicoplanin with a target trough concentration of 20 μg/mL using a regimen of 12 mg/kg for five doses within the initial 3 days

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Abstract

Background: A trough concentration (C_{min}) ≥20 μg/mL of teicoplanin is recommended for the treatment of serious methicillin-resistant *Staphylococcus aureus* (MRSA) infections. However, sufficient clinical evidence to support the efficacy of this target C_{min} has not been obtained. Even though the recommended high C_{min} of teicoplanin was associated with better clinical outcome, reaching the target concentration is challenging.

Methods: Pharmacokinetics and adverse events were evaluated in all eligible patients. For clinical efficacy, patients who had bacteremia/complicated MRSA infections were analyzed. The primary endpoint for clinical efficacy was an early clinical response at 72–96 h after the start of therapy. Five dosed of 12 mg/kg or 10 mg/kg was administered as an enhanced or conventional high loading dose regimen, respectively. The C_{min} was obtained at 72 h after the first dose.

Results: Overall, 512 patients were eligible, and 76 patients were analyzed for treatment efficacy. The proportion of patients achieving the target C_{min} range (20–40 μg/mL) by the enhanced regimen was significantly higher than for the conventional regimen (75.2% versus 41.0%, $p < 0.001$). In multivariate analysis, C_{min} ≥20 μg/mL was an independent factor for an early clinical response (odds ratio 3.95, 95% confidence interval 1.25–12.53). There was no significant difference in the occurrence of adverse events between patients who did or did not achieve a C_{min} ≥20 μg/mL.

Conclusion: A target C_{min} ≥20 μg/mL might improve early clinical responses during the treatment of difficult MRSA infections using 12 mg/kg teicoplanin for five doses within the initial 3 days.

Background

Teicoplanin is a glycopeptide antibiotic used for the treatment of methicillin-resistant *Staphylococcus aureus* (MRSA). Teicoplanin inhibits peptidoglycan polymerization, resulting in the inhibition of bacterial cell wall synthesis and cell death [1]. This antibiotic is currently available in many countries in Europe, Asia, and South America but not in the United States. Approximately 90% of teicoplanin bound to serum albumin and is present at high levels in tissues, which may explain its long half-life (83–168 h). Because steady state is generally achieved in five half-lives, 14 days of repeated administration is required to reach 93% of the concentration at steady state [2]. Therefore, a loading dose of teicoplanin is required to achieve early optimal serum levels [3]. The ratio of the area under the concentration-time curve to the minimum inhibitory concentration (AUC/MIC) was used to determine the pharmacokinetic/pharmacodynamic (PK/PD) index associated with teicoplanin therapy [4]. In a clinical setting, the trough concentration (C_{min}) is used as a surrogate marker to predict adequate treatment effects [5]. Although the C_{min} is recommended to be obtained 4 days after the start of therapy, it might be acceptable to perform therapeutic drug monitoring (TDM) within 3 days in cases of low renal function.

Traditionally, a C_{min} ≥10 μg/mL is considered appropriate for MRSA infections [6]. Recently, it was reported that a teicoplanin C_{min} ≥15 μg/mL was required for the successful clinical treatment of MRSA infection [7, 8], whereas a C_{min} ≥20 μg/mL was recommended for other serious infections such as bone and joint infections and infective endocarditis [9, 10]. Wilson et al. [9] showed that treatment in 6/10 staphylococcal infective endocarditis patients failed if the C_{min} was <20 μg/mL compared with 1/11 where the C_{min} was ≥20 μg/mL. Byrne et al. [11] reported that the mean C_{min} on days 3–7 in successful cases was 19.6 mg/L, suggesting that a target C_{min} ≥20 mg/L would be required for the clinically acceptable probability of a successful outcome. However, Harding et al. [12] reported that with the standard dose, most patients had a C_{min} <15 μg/mL; therefore, they could not conclude that a C_{min} ≥20 μg/mL would add further benefit. Byrne et al. [11] reported that although their hospital adopted higher than conventional doses in patients with hematological malignancy with the aim of achieving a C_{min} ≥20 μg/mL, attainment of the target concentration in the first week of therapy was poor.

A dosing regimen of teicoplanin to reach a C_{min} ≥20 μg/mL should be used for patients with severe, deep-seated or complicated MRSA infections. For bone and joint infections and infective endocarditis, teicoplanin 12 mg/kg body weight every 12 h for three-to-five doses is recommended [6]. In Monte Carlo simulations, a high probability of attaining the target C_{min} of 20 μg/mL was observed using a regimen of 12 mg/kg administered at 12-h intervals for five doses, but not when using four doses [13]. Byrne et al. [14] reported the recommended loading dose to achieve a C_{min} ≥20 μg/mL based on population PK analysis was 12 mg/kg administered every 12 h for five doses in patients with a body weight of 70 kg and serum albumin level of 3.0 mg/dL. This enhanced loading dosing regimen was considered optimal on the basis of these simulation analyses. Taken together, sufficient clinical data to support C_{min} ≥20 μg/mL have not been obtained. Even though the recommended high C_{min} of teicoplanin appeared to be associated with a better clinical outcome, reaching the target concentration is challenging. Regimens to attain this target concentration have only been suggested by PK/PD analyses. The aim of this study was to evaluate the clinical efficacy and safety when the target teicoplanin C_{min} was set as ≥20 μg/mL in patients with complicated MRSA infections including bacteremia using a loading dose regimen of 12 mg/kg administered every 12 h for five doses.

Methods

Patients

This retrospective study was conducted between June 2015 and May 2019, and was approved by the Institutional Review Board of Hyogo College of Medicine (No. 3266). Adult patients who were treated with teicoplanin, and in whom TDM was performed, were included in the study. Exclusion criteria were patients with known hypersensitivity to teicoplanin, pregnancy, below the age of 18 years, and requirement of intermitted hemodialysis and continuous renal replacement therapy. The analysis of C_{min} and the safety population included all eligible patients. The analysis of the clinical efficacy population included patients 1) who had bacteremia or complicated infections [ventilator associated pneumonia (VAP), osteomyelitis

and arthritis infection, and central nervous system infection] by MRSA, 2) who received at least 4 days of teicoplanin treatment, 3) who did not receive any concomitant antibiotics with anti-MRSA activity, and 4) who did not receive the above mentioned antibiotics for > 24 h within the previous 3 days.

A diagnosis for each infection was based on definitions in the guidelines issued by the National Healthcare Safety Network [13]. Infections with at least one of the following signs were analyzed: core temperature >37.8°C, total peripheral white blood cell (WBC) count >10,000/mm^3, or C-reactive protein (CRP) >3.0 mg/dL. The minimum inhibitory concentration (MIC) of teicoplanin was measured by microdilution methods in accordance with the Clinical and Laboratory Standards Institute testing guidelines (M02 and M07, 2018) [14]. MIC break-points set by the European Committee on Antimicrobial Susceptibility Testing were adopted in this study, and antimicrobial resistance was defined as MIC ≥4 μg/mL. The estimated glomerular filtration rate (eGFR) was calculated using the following formula developed by the Japanese Society of Nephrology [eGFR (mL/min/1.73 m^2) = 194 × serum creatinine $^{(-1.094)}$ × age $^{(-0.287)}$ × 0.739 (for females)] [17].

Administration plan in patients with conventional and enhanced high loading dose regimens

The target initial C_{min} was 15–30 μg/mL between June 2015 and May 2018, and 20–40 μg/mL in patients with bacteremia/complicated MRSA infections between June 2018 and May 2019. In accordance with these target C_{min} values, we conducted two different teicoplanin dose regimens for 3 consecutive days (Table 1). A conventional high loading dose regimen was used for patients with a target C_{min} 15–30 μg/mL, and an enhanced high loading dose regimen was used for patients with a target C_{min} 20–40 μg/mL.

Conventional high loading dose regimen for patients with eGFR ≥60 mL/min/1.73 m^2: a loading dose of 10 mg/kg (actual body weight) twice daily on the first and second days, followed by 10 mg/kg once daily on the third day. Maintenance dosing after the fourth day was 6.7 mg/kg once daily. Loading and maintenance dose was adjusted according to renal function (Table 1). Enhanced high loading dose regimen for patients with eGFR was ≥60 ml/min/1.73 m^2: a loading dose of 12 mg/kg twice daily on the first and second days, followed by 12 mg/kg once daily on the third day The maintenance dosing regimen after the fourth day was 6.7 mg/kg once daily. Loading and maintenance dose was adjusted according to renal function (Table 1).

Therapeutic drug monitoring and dosage adjustment

An initial C_{min} sample was obtained prior to the administration of teicoplanin on the fourth day (at 72 h after the first dose). The target C_{min} was defined as 20–40 μg/mL. The dose of teicoplanin was adjusted according to the initial C_{min}. Additional loading doses were administered on the fourth day if the initial C_{min} was lower than the target C_{min}. Blood samples were collected in blood-collection tubes without a blood coagulation accelerator and immediately centrifuged at 3000 rpm for 10 min. Teicoplanin was

measured using a fluorescence polarization immunoassay with a TDXFLX analyzer (Abbott Japan Co., Tokyo, Japan) and a teicoplanin TDM kit-IBL (OXIS International Inc., Beverly Hills, CA, USA).

Clinical efficacy

The primary endpoint was an early clinical response at 72–96 h after the start of teicoplanin therapy. We defined patients as responders if they had a 30% or greater decrease in total peripheral WBC count or CRP, decline of fever (defined as a daily maximum temperature decrease of > 0.3°C for at least two consecutive days in febrile patients), without worsening of clinical features, and did not die within 96 h [18]. Secondary efficacy end points were clinical success at the end of teicoplanin therapy (EOT), which was defined as survival with the resolution or improvement of all core symptoms and signs of infection in each infection to the extent that further antibacterial therapy with anti-MRSA activity was unnecessary. Microbiological assessments were conducted using cultures taken before the start of teicoplanin administration and at the completion of treatment, and microbiological success was defined as “eradication” (pathogen absent in culture) or “presumed eradication” (no material available for culture because the infection was cured or attenuated).

Adverse events

Adverse events of nephrotoxicity and hepatotoxicity were evaluated on the fourth day of therapy and at the end of teicoplanin therapy. Nephrotoxicity was defined as a serum creatinine (Cre) increase >0.5 mg/L or 50% increase from the baseline [19]. Hepatotoxicity was defined as aspartate aminotransferase (AST) or alanine aminotransferase (ALT) levels at or above three times the upper limit of normal. If the AST or ALT baseline was abnormal, hepatotoxicity was defined as AST or ALT at or above three times the baseline [20].

Statistical analysis

Parametric variables were analyzed using the Student’s *t*-test, while nonparametric variables were analyzed using the Mann–Whitney *U*-test or Fisher’s exact test. Multivariate analyses were performed to determine the odds ratio (OR) to achieve the target C_{min} (≥20 μg/mL) and early clinical responses. The crude OR in univariate analysis was estimated for each variable using the chi-squared test, and potential confounders were examined by cross tabulation. Variables selected by univariate analysis ($p < 0.1$) were subsequently entered into a stepwise logistic regression model to estimate the magnitude of association [adjusted OR and 95% confidence interval (CI)]. The level of significance was set at $p < 0.05$. SPSS ver. 24 (SPSS Inc., Chicago, IL, USA) was used to perform statistical analyses.

Results

Patient characteristics

The number of patients included in the analysis of C_{min} and the safety population was 512 (363 in the high loading dose regimen group and 149 in the enhanced high loading dose regimen group). Among 139 patients with MRSA infections, 63 were excluded from the efficacy population [26 because of the previous use of antimicrobial agents with anti-MRSA activity and 37 without bacteremia/complicated MRSA infections (skin and soft tissue infection = 21; intra-abdominal infection = 12; urinary tract infection = 4; and sinusitis = 1)]. Thus, 76 patients with bacteremia/complicated MRSA infections were analyzed for treatment efficacy (53 in the high loading dose regimen group and 23 in the enhanced high loading dose regimen group). Teicoplanin MICs were ≤2 μg/mL in all MRSA isolates, and there was no resistant strain. Baseline demographics of enrolled patients with the conventional and enhanced high loading dose regimens are shown in Table 2. The total doses for the initial 3 days and the maintenance dose after day 4 according to renal function in patients with conventional and enhanced high loading dose regimens are shown in supplemental table 1. The recommended doses and observed administered doses in this study were similar in each renal function category.

Measurements of C_{min}

The median C_{min} on the fourth day was 18.3 μg/mL in the conventional high loading dose regimen group, and 24.9 μg/mL in the enhanced high dose loading regimen group ($p < 0.001$) (Table 3). A similar difference was confirmed in each renal function category (Supplementary table 2). The proportion of patients achieving the target range (20–40 μg/mL) in the enhanced high loading dose regimen was significantly higher than that in the conventional high loading dose regimen (75.2% versus 41.0%, $p < 0.001$). Even in the enhanced high loading dose regimen group, only 5 of 149 patients had a C_{min} ≥40 μg/mL and no patient experienced a C_{min} ≥60 μg/mL. Additional loading doses were administered if the initial C_{min} was <20 μg/mL (25 of 32 patients, 78.1%). However, the target C_{min} was ≥15 μg/mL in the conventional high loading dose regimen, and additional loading doses were administered if the initial C_{min} was <15 μg/mL (56 of 85 patients, 65.9%).

In the multivariate analysis, enhanced high loading dose regimen (adjusted OR: 7.75, 95% CI: 4.62–13.00) and body mass index ≥25 (adjusted OR: 2.33, 95% CI: 1.24–4.38) were independent factors to achieve an initial C_{min} ≥20 μg/mL. In contrast, hypoalbuminemia (adjusted OR: 0.24, 95% CI: 0.15–0.37), total parenteral nutrition (adjusted OR: 0.54, 95% CI: 0.32–0.92), and surgery within 28 days (adjusted OR: 0.47, 95% CI: 0.30–0.74) decreased the attainment of an initial C_{min} ≥20 μg/mL (Table 4). Although the cut off serum albumin concentration was defined as the median value for hypoalbuminemia, the median C_{min} according to each serum albumin concentration category were 25.7 μg/mL in the ≥3.5 g/dL group; 22.0 μg/mL in the 3.0–3.5 g/dL group; 21.6 μg/mL in the 2.5–3.0 g/dL group; 18.2 μg/mL in the 2.0–2.5 g/dL group; and 16.2 μg/mL in the <2.0 g/dL group. There was a tendency toward a dose response relationship between C_{min} and serum albumin level.

Clinical efficacy of teicoplanin therapy in patients with complicated MRSA infection

Fifty-four of 76 patients (71.1%) met the definition for an early clinical response on the fourth day, and 55 of 76 patients (72.4%) met the definition of clinical success at the end of the therapy. The early clinical response rate in patients with an initial C_{min} ≥20 μg/mL tended to be higher than those with a C_{min} <20 μg/mL [31/39 (79.5%) versus 23/37 (62.2%), p = 0.096]. However, there was no significant difference in clinical success at the end of therapy between patients who did and did not achieve an initial C_{min} ≥20 μg/mL. The maximum C_{min} during therapy and the type of regimen did not affect any patient outcomes (Table 5, supplementary table 3). In the multivariate analysis, an initial C_{min} ³20 μg/mL (adjusted OR: 3.95, 95% CI: 1.25–12.53) and bacteremia (adjusted OR: 4.55, 95% CI: 1.10–18.77) were independent factors for an early clinical response to teicoplanin therapy (Table 6).

Adverse events related to teicoplanin therapy

In the population used for the assessment of safety, there were no significant differences in the occurrence of adverse events on the fourth day and at the end of therapy between those patients who did and did not achieve an C_{min} ≥20 μg/mL (nephrotoxicity: 2.9% versus 3.4%, p = 0.739, and 7.8% versus 7.9%, respectively; hepatotoxicity: 1.6% versus 1.5%, p = 1.000, and 2.9% versus 1.5%, p = 0.366, respectively) (Table 6). There was no significant difference in the occurrence of adverse events between the two teicoplanin regimens (supplementary table 4).

Discussion

Although it appears that teicoplanin C_{min} ≥15 μg/mL is required for clinical success in the majority of MRSA infections [7, 8]. C_{min} ≥20 μg/mL is recommended for serious infections such as infective endocarditis and bone and joint infections. However, the recommendation of this high target C_{min} was based on case-control studies of a small number of patients and statistical analyses were often difficult. To the best of our knowledge, this is the first study to draw the conclusion with the multivariate analyses. Initial C_{min} ³20 μg/mL (adjusted OR: 3.95) was an independent factor for the early clinical response to teicoplanin therapy. However, there was no significant difference in clinical success at the end of therapy between patients who did and did not achieve an initial C_{min} ≥20 μg/mL, possibly because of dose modifications based on the initial C_{min}.

For infective endocarditis and bone and joint infections, teicoplanin 12 mg/kg body weight every 12 h for three to five doses was recommended to achieve a target C_{min} ≥20 μg/m [6]. However, the optimal number of loading doses is unclear. In general, population PK analyses and Monte Carlo simulations are conducted to assess the teicoplanin dosage regimens associated with a high probability of achieving the target C_{min} [13, 14]. In these PK simulation studies, the sample size is small for clinical studies and therefore no conclusions about the clinical implications are possible. Previously, we demonstrated that a C_{min} 15–30 μg/mL was obtained in 68% of patients (mean body weight approximately 50 kg) with a dosing regimen of 600 mg at 12-h intervals for five doses (total dose of 3000 mg) [8]. However, the mean

C_{min} remained 20.0 μg/mL, and post-hoc analysis revealed that a target C_{min} ≥20 μg/mL was obtained in less than half of the patients.

In a regimen of 12 mg/kg every 12 h for four doses followed by 6 mg/kg once daily, the total dose over 3 days was 54 mg/kg (2700 mg in patients weighing 50 kg), which was less than the total dose of 3000 mg in the regimen using 600 mg for five doses. Therefore, in this study we decided to use 12 mg/kg for five doses in patients with difficult MRSA infections to achieve a target C_{min} ≥20 μg/mL. With this enhanced high loading dose regimen, a significantly higher achievement rate of the target C_{min} 20–40 μg/mL was observed compared with the conventional regimen (75.2% versus 41.0%, $p < 0.001$). Even with the enhanced loading dose, only a small number of patients had a C_{min} >40 μg/mL and no patients experienced a C_{min} >60 μg/mL, which might cause adverse events related to teicoplanin therapy. Because of the adequate teicoplanin concentration, the enhanced loading dose regimen did not result in a high rate of adverse events compared with the conventional loading dose regimen.

In the multivariate analysis, enhanced regimen and body mass index ≥25 were independent factors associated with a C_{min} ≥20 μg/mL. In contrast, hypoalbuminemia, total parenteral nutrition, and surgery were selected as independent factors for the decreased attainment of a C_{min} ≥20 μg/mL. Several factors other than dosing regimen affected the teicoplanin concentration. There was significant interpatient variability in teicoplanin PK which complicates the empiric approach to dosing, suggesting the need for TDM. On the basis of a PK study of healthy volunteers, multiple-dose teicoplanin administration from 3 to 12 mg/kg of body weight showed a linear dose-serum concentration relationship [21]. However, the dose-serum concentration in critically ill patients can be highly variable [22-24]. Serum albumin concentrations are an important determinant of PK for antibiotics that have a high binding affinity to albumin such as teicoplanin. Lower albumin concentrations were associated with a higher free (unbound) fraction of antibiotic [25], which increases the distribution and clearance of the drug leading to a reduced total drug concentration [26]. Byrne et al. [14] reported that a low serum albumin concentration was associated with the reduced probability of attaining the target total, but not free, C_{min}, which is responsible for antimicrobial activity. Dosing regimens for teicoplanin have been determined according to total C_{min} targets that may not be appropriate for patients with hypoalbuminemia.

There were several limitations in our study. First, this study was conducted retrospectively in a single institution. Second, observer bias should be considered. To limit the bias, a clear rule for clinical success was defined. Third, central catheter-related blood stream infections were included in this study, and a different result may have been obtained for clinical efficacy if only patients with complicated MRSA infections, such as infective endocarditis and bone and joint infections, were analyzed. Fourth, more measurements are required to assess when the target C_{min} was actually achieved in the evaluation of clinical efficacy at the end of therapy. Fifth, plasma concentration time curves were not evaluated to support the data obtained. The AUC is an extremely useful parameter in PK models. In vancomycin, use of AUC determined using a Bayesian approach is recommended to optimize dosing. Lastly, the maintenance dose might be relatively low in our study, which might affect the clinical efficacy at the end

of therapy. Lee et al. [27] demonstrated that significantly higher favorable final clinical response rates were found in patients who received a loading dose followed by increased maintenance doses of 6 mg/kg/12 h. than those with standard maintenance doses of 6 mg/kg/24h.

Conclusion

In conclusion, a higher target initial C_{min} ≥20 μg/mL is likely to be associated with a better early clinical response for the treatment of bacteremia/complicated MRSA infections. Although tree to five doses of teicoplanin 12 mg/kg body weight every 12 h is usually used for bone and joint infections and infective endocarditis, only a regimen of five doses is recommended to reach the optimal C_{min}.

Declarations

Ethics approval and consent to participate The study was approved by the Institutional Review Board of Hyogo College of Medicine (No. 3266). The institutional review board waived the requirement for informed consent from patients included in this study.

Consent for publication Not applicable.

Availability of data and materials The dataset was presented within the additional supporting files.

Competing interests Y. Takesue received grant support from Shionogi & Co., Ltd., and payment for lectures from Astellas Pharma Inc., and MSD Japan. Other authors have no conflict of interest to declare.

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Authors' contributions TU was involved in the conception of the study, collection, analysis and interpretation of data, the creation of new software used in the work, draft the work and substantively revised of the manuscript. Y Takesue was involved in the design of the study and draft the work. KN, K Ichiki, K Ishikawa, Y Takai, KY, YW, TT, NO, Y Takahashi, MI, ST, HI, MU and TK contributed to the data collection and interpretation. All authors had substantial input to the drafting and review of the manuscript and approved the final version prior to publication.

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Tables

Due to technical limitations the Tables are available as a download in the Supplementary Files.

Supplementary Files

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