Randomized Comparison of Serum Teicoplanin Concentrations following Daily or Alternate Daily Dosing in Healthy Adults

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Teicoplanin is a glycopeptide antibiotic which has been extensively evaluated as a treatment for serious, invasive infections caused by gram-positive bacteria (17) and is marketed in different countries. It is a mixture of five closely related components with similar polarities and biological activities. It is characterized by a long elimination half-life, found to be between 30 and 180 h (8, 16). The linearity of teicoplanin pharmacokinetics after administration of a single dose, especially in the range of 15 to 25 mg/kg of body weight (4), together with its excellent safety profile up to doses of 12 mg/day (17), suggests that an alternate-day administration schedule could be considered.

The present teicoplanin dosing recommendations suggest that a predose (trough) concentration in serum of at least 10 mg/liter should be maintained (9). However, trough concentrations >20 mg/liter are considered optimal for the treatment of staphylococcal endocarditis and other severe staphylococcal infections when it is used as monotherapy and/or in immunosuppressed patients (12, 17). The use of an appropriate loading dose is recommended to achieve earlier therapeutic concentrations, especially in patients with severe infections (11, 15).

An alternate-day dosing schedule has already been studied in patients with chronic osteomyelitis or endocarditis (7, 10). Teicoplanin was administered three times a week (Mondays, Wednesdays, and Fridays) on an outpatient basis after loading doses were delivered by daily administration in the hospital.

The individual doses were adjusted once weekly (on Mondays) in order to achieve stable trough concentrations in serum of approximately 10 mg/liter for the treatment of osteomyelitis and 20 mg/liter for the treatment of endocarditis, the recommended target concentrations for these types of infections (12, 17). Thirty-seven of 44 (84%) patients with osteomyelitis and 8 of 10 (80%) patients with endocarditis were treated successfully. Adverse events were observed in nine patients. While these studies indicated the feasibility of such a drug administration schedule and confirmed that the objectives for the trough concentration in serum could be reached, they were not designed to include a pharmacokinetic analysis.

Consequently, it was believed that it was necessary to study the pharmacokinetics of teicoplanin with alternate-day administration in a study under controlled conditions with healthy volunteers. The primary objective of this study was to compare the pharmacokinetics of teicoplanin when it was administered on alternate days with the pharmacokinetics of the drug when it was administered daily to healthy adult volunteers. The comparison was based on the trough concentrations in serum at the end of 10 days of administration. A secondary objective was to determine the bactericidal activity of the serum of the subjects in both groups against a range of Staphylococcus aureus strains at the time of the trough concentration on days 3 (after the loading doses) and 11 (at the end of the treatment period).

MATERIALS AND METHODS

Study subjects and procedures. This study was a single-center, randomized, open-label, parallel-group, controlled trial with 24 healthy volunteers. Healthy young adult (age range, 18 and 35 years) male volunteers with body mass indices between 18 and 24 kg/m², a normal physical examination, normal transaminase levels, an estimated creatinine clearance of at least 80 ml/min by use of the Cockcroft and Gault formula (3), and a normal electrocardiogram (ECCG) were considered for inclusion; further inclusion criteria were a negative urine screen for opiates and other drugs, the absence of serum indicators of hepatitis B and C, and no history of prior hypersensitivity to vancomycin and teicoplanin. A 2:1 randomization into groups 2 and 1, respectively, was planned to optimize data collection for the dose tested.

The subjects were screened prior to study admission by use of the criteria outlined above. The screening visit also allowed the collection of baseline data for the safety evaluations conducted during and at the end of treatment. After the subjects provided informed consent, they were randomized. The subjects were hospitalized in the ITEC Pharmacology facility (Hôpital des Peupliers, Paris, France) during the entire course of the study (11 days) for study medication infusions, medical supervision, blood sampling for teicoplanin assays, and assessments of clinical and biological safety.

Selection of dose regimens tested and constitution of the groups. The dose regimen tested was selected on the basis of the indications from a simulation conducted with the Rowland model (16), the objective of which was to obtain a trough concentration in serum of at least 10 mg/liter. This value was considered the lower bound of a bilateral 95% confidence interval of the mean. By assuming a 15% interassay and intrasubject coefficient of variation (CV) according to the data previously published by Pec et al. (14), a mean value of 14.3 mg/liter with a 30% confidence interval was targeted for the simulation, thereby ensuring that 97.5% of the individual trough concentrations would be at least 10 mg/liter. Another objective of the simulation was to ensure that therapeutic concentrations were reached as soon as after the first infusion.

A computer simulation of various intravenous administration schedules was performed by using the equation described by Rowland (16): \[ c = D \left( 8.9 \times 10^{-1} + 1.93 \times 10^{-7} t + 0.43 \times 10^{-4} t^2 \right), \] where \( c \) is the mean concentration in serum (in milligrams per liter), \( D \) is the teicoplanin dose (in milligrams per kilogram of body weight), and \( t \) is the time (in hours). The pharmacokinetics of teicoplanin (4, 16) were assumed to be linear (no dose or time dependency), and the final concentration was the sum of all concentrations reached with all preceding administrations.

The simulation indicated that a mean concentration of 14.3 mg/liter could be reached by administration of a 15-mg/kg dose on alternate days and that administration of loading doses of 12 mg/kg three times every 12 h allowed therapeutic concentrations to be reached as soon as after the first infusion.

Daily dosing with 6 mg/kg, with administration of 6 mg/kg twice a day on the first day, was used as the reference regimen (11). The computer simulation also indicated that this regimen would achieve similar trough values.

Two treatment groups were developed. Group 1 received 6 mg/kg intravenously every 12 h three times and then 6 mg/kg per day from days 3 to 10, and group 2 received 12 mg/kg intravenously every 12 h three times and then 15 mg/kg every other day on days 3, 5, 7, and 9.

Teicoplanin dosing and sampling times. The teicoplanin dosing schedules described above were used; 400-mg freeze-dried teicoplanin-containing vials (batch A0007; Gruppo Lepetit, Anagni, Italy) with a 24-mg sodium chloride described above were used; 400-mg freeze-dried teicoplanin-containing vials (batch A0007; Gruppo Lepetit, Anagni, Italy) with a 24-mg sodium chloride

Statistical analysis. The inclusion of 24 subjects (16 subjects in group and 8 subjects in group 2) allowed the noninferiority analysis to have 77% power, based on the Hodges-Lehmann 95% confidence interval for the differences in residual serum teicoplanin concentrations by assuming a normal distribution, a 1-mg/liter standard deviation, and a 1.3-mg/liter acceptable difference, according to the experience of Pea et al. (14).

The primary analysis variable was the residual serum teicoplanin concentration measured on day 11, i.e., the value at 24 h postdosing in group 1 and the value at 48 h postdosing with the 15-mg/kg dose in group 2. A nonparametric method was used for comparison due to the small numbers of measures. The 95% confidence interval for the difference between the two treatments was thus calculated by the nonparametric Hodges-Lehmann method described by Garder and Altman (6), among others. If the lower limit of the confidence interval of the difference in the concentrations (concentration for group 2 – concentration for group 1) was equal to or greater than an acceptable difference of 1.3 mg/liter, the treatment for group 2 would be considered noninferior to that for group 1. All other data (trough concentrations on any other day, middose concentrations in group 2, and the concentration at 1 h postdosing) were described and are expressed as means and standard deviations (SDs). Individual trough concentrations were examined with regard to the potential differences from the recommended target concentration of 10 mg/liter. For the comparability of the groups, the baseline demographic characteristics were compared by a Wilcoxon test.

Repeated-measurements analyses of variance were performed for group 1 by using the individual values of the residual (trough) concentrations in serum from days 3 to 11 and for group 2 by using the trough concentrations at 48 h postdosing on days 5, 7, 9, and 11 and the trough concentrations at 24 h postdosing on days 3, 4, 6, 8, and 10. In the model, Bonferroni multiple pairwise comparisons of the effect of the day of treatment were performed within groups in order to determine whether the steady state was reached by or before day 11.

A rough estimation of the area under the concentration-time curve (AUC) at steady state from day 9 to day 11 (AUC₉₋₁₁) was performed by using the trapezoidal rule over two 1-h postdosing concentrations (days 9 and 10) and two trough concentrations (days 10 and 11) or one postdosing concentration value (day 9), one trough concentration middose (day 10), and one trough concentration (day 11), by group.

Bactericidal activity of serum. The bacterial strains used in the study (seven S. aureus strains) were first characterized: the MICs for the strains were determined by microdilution in Mueller-Hinton broth (MHB) with an inoculum of 10⁶ CFU/ml. The MIC was defined as the first dilution with no visible growth. The MICs ranged from 0.5 to 8 mg/liter, including an MIC of 4 mg/liter for S. aureus 5017 and an MIC of 8 mg/liter for S. aureus 152 (see Table 2). The MICs were also determined in buffered pooled human serum and in an ultrafiltrate (obtained by ultrafiltration through a Macrocept membrane with a 30-kDa threshold).

In this case the MIC was defined as the first dilution with a bacterial count of 10⁶ CFU/ml, as the turbidities of the sera and ultrafiltrates did not allow direct reading of the MICs. The MICs in whole human serum ranged from 2 to 16 mg/liter and were two to four times higher than those in broth; in the corresponding serum ultrafiltrate, the MICs ranged from 1 to 16 mg/liter and were one to two times higher than those in serum (see Table 2).

The bactericidal activities of the sera of the subjects were determined by using the sera drawn for determination of trough concentrations on day 3 (at the end of the loading-dose period) and day 11 (24 or 48 h after administration of the last dose, depending on the group). Whole serum was tested in order to measure the activity of total teicoplanin as it is present in serum. The sera were inoculated with 10⁷ to 10⁹ CFU at time zero; and viable strain counts were determined after 18 to 24 h of contact. The results are expressed as the log₁₀ bacterial counts (CFU/ml) and the bactericidal activities are expressed as the changes in the log bacterial concentrations (the changes between 4 h and time zero, 8 h and time zero, and 24 h and time zero) The bactericidal activity in the ultrafiltrate sera (obtained by ultrafiltration through a Macrocept membrane with a 30-kDa threshold, as described above) was also measured by the same method.

For all strains, the individual changes in the log concentrations in the sera of all subjects (both groups taken together) were graphically plotted versus the concentrations measured in the corresponding sera to determine a possible correlation between bactericidal activity and the concentrations measured in serum.
Safety evaluation. Safety and tolerance were evaluated throughout the study until day 11, with special attention given to blood pressure, heart rate, local infusion site reactions, and systemic hypersensitivity reactions. Hematology and serum biochemistry parameters, including liver enzyme activity and serum creatinine concentrations, were also measured throughout the study. All values were evaluated according to the normal ranges at the ITEC Pharmacology center. Individual values before treatment (screening) and after treatment (day 11) were compared by a signed-rank test in order to determine trends. An ECG and a normal tone audiometry examination were performed before and at the end of the treatment.

Ethical and legal issues. The study was performed in accordance with the Declaration of Helsinki and the regulations in force in France concerning studies with subjects without individual (direct) benefit.

RESULTS

All patients were young healthy male volunteers. The demographic characteristics of the subjects and the values of selected biological parameters for the subjects at screening are presented in Table 1 and were homogeneous between groups ($P > 0.05$). The dose of teicoplanin infused was strictly weight adjusted (6, 12, or 15 mg/kg). The total doses received were 66 mg/kg for subjects in group 1 and 96 mg/kg for subjects in group 2.

The mean ± SD trough concentrations in serum on day 11 were 16.0 ± 2.1 and 17.9 ± 3.5 mg/liter in groups 1 and 2, respectively. The 95% confidence interval of the difference (−0.2, 3.6 mg/liter) obtained by a nonparametric test indicated a non-inferiority of the treatment for group 2 versus that for group 1.

A graphical representation of the mean serum teicoplanin concentrations at 1 h postdosing and the trough concentrations from the day of the first infusion (day 1) to the trough concentration on the last day (day 11) for groups 1 and 2 are presented in Fig. 1.

For group 1, the mean ± SD concentrations in serum were 38.2 ± 6.7 mg/liter 1 h after the first infusion and 58.2 ± 11.9 mg/liter after the third (and last) infusion of the loading dose on day 2. It was then relatively stable, on the order of 55 to 60 mg/liter up to day 10. The mean ± SD trough concentrations in serum were 14.1 ± 2.9 mg/liter on day 2 (24 and 12 h after the first and second infusions of the loading doses, respectively) and 12.5 ± 2.8 mg/liter on day 3 (24 h after the third infusion of the loading dose). It slowly increased to reach 16.1 ± 4.2 mg/liter on day 7 and was then relatively stable until day 11.

For group 2, the mean ± SD concentrations in serum 1 h after the first infusion of the loading dose and then reached 120.3 ± 18.4 mg/liter after the third infusion of the loading dose on day 2. It was then relatively stable, on the order of 115 to 125 mg/liter up to day 9. The mean ± SD trough concentrations in serum were 29.8 ± 6.8 mg/liter on day 2 (24 and 12 h after the first and second infusion of the loading dose) and 45.3 ± 10.2 mg/liter on day 11. The mean ± SD concentrations in serum at 1 h postdosing and the trough concentrations from the day of the first infusion to the trough concentration on the last day (day 11) for groups 1 and 2 are presented in Fig. 1.

![FIG. 1. Serum teicoplanin concentrations (mean ± SD) determined by fluorescence polarization immunoassay. ●, 15-mg/kg dose; ■, 6-mg/kg dose.](http://aac.asm.org/)

### TABLE 1. Demographic and biological characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Group 1 (n = 8 subjects)</th>
<th>Group 2 (n = 16 subjects)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>26.1 (20–34)</td>
<td>24.2 (20–33)</td>
</tr>
<tr>
<td>Wt (kg)</td>
<td>74.8 (59–99)</td>
<td>69.0 (65–76)</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>22.6 (20–26)</td>
<td>21.7 (20–23)</td>
</tr>
<tr>
<td>Serum creatinine conc (μmol/liter)</td>
<td>84.6 (76–95)</td>
<td>90.8 (80–104)</td>
</tr>
<tr>
<td>Estimated creatinine clearance (ml/min)</td>
<td>123.7 (91–149)</td>
<td>110.0 (91–127)</td>
</tr>
<tr>
<td>Alkaline phosphatase level (IU/liter)</td>
<td>61.4 (39–79)</td>
<td>64.4 (44–96)</td>
</tr>
</tbody>
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* All subjects were men. The values are means (minima-maxima).
infusions of the loading doses, respectively) and 27.7 ± 6.0 mg/liter on day 3 (24 h after the third infusion of the loading dose). The mean ± SD concentrations were 31.8 ± 6.9 and 19.5 ± 4.2 mg/liter on days 4 and 5, respectively (middose and trough concentrations, respectively) and were then relatively stable until days 10 and 11.

The individual concentrations in serum exceeded 10 mg/liter in all subjects at all time points and exceeded 15 mg/liter in all except two subjects: in one subject on days 9 and 11 (12.7 and 13.5 mg/liter, respectively) and in another subject on days 7 and 9 (13.0 and 13.8 mg/liter, respectively). The middose concentrations (on days 4, 6, 8, and 10) exceeded 20 mg/liter in all except one of the subjects at all time points; the exception was the second subject mentioned above, for whom the middose concentration was 19.1 mg/liter on day 6 (data not shown).

The concentrations in serum measured in individuals in group 1 (data not shown) were inferior to those measured in individuals in group 2, particularly on the days in which the middose levels were measured in group 2 (days 4, 6, 8, and 10). In both groups, however, they consistently exceeded the 10-mg/liter target concentration.

The analysis of variance was performed after the exclusion of one outlier from each group (a trough concentration of 34.8 mg/liter measured on day 10 in a subject in group 1 [trough concentrations, 16.9 and 17.0 mg/liter on days 9 and 11, respectively] and a middose concentration of 51.8 mg/liter measured on day 6 in a subject in group 2 [middose concentrations, 29.5 and 26.3 mg/liter on days 4 and 8, respectively]). The analysis of variance showed an effect of time. Multiple comparisons showed no significant differences in concentrations between days from days 5 to 11 for group 1 and from days 6 or 7 to 11 for group 2. Consequently, steady-state levels were considered to have been reached by day 5 in group 1 and by day 6 or 7 in group 2.

The mean estimated AUC9–11 values were 2,282 and 1,783 mg h/liter for group 2 and group 1, respectively, with a ratio of the mean AUC9–11 values of 1.28. This ratio is close to the ratio of 1.25 for the total infused doses of teicoplanin during this 2-day period in both groups (15 mg/kg and twice 6 mg/kg for groups 1 and 2, respectively).

The sera of all subjects, sampled at the time of the trough concentrations on day 3 and day 11, were observed to have bactericidal activity against all S. aureus strains tested with the exception of S. aureus strain 1952 (teicoplanin MICs, 8 mg/liter in MHB and 16 mg/liter in serum) after 8 and 24 h of exposure. The mean changes in the log bacterial counts after 8 and 24 h of exposure are presented in Table 2. The bactericidal activity appeared to be strain dependent but not concentration dependent against all strains except S. aureus strain 1952. As a consequence, the mean change in the log bactericidal counts was calculated for each strain except strain 1952. The mean change in the log bacterial counts ranged from −1.8 to −2.8 (between 8 h and time zero) and −2.3 to −3.3 (between 24 h and time zero) according to the strain. No bactericidal activity was observed in the ultrafiltrate, regardless of the strain, including the S. aureus strains for which MICs in this medium are low (Table 2).

Figures 2 and 3 illustrate the bactericidal activities (changes in log bacterial counts between 24 h and time zero) of the sera against a selected strain (S. aureus 6017) for which the MIC was 4 mg/liter and S. aureus strain 1952, respectively, with the change in bacterial counts log plotted against the corresponding concentration measured in serum. Bacteriostatic and bactericidal activities were not consistently observed against S. aureus strain 1952. In fact, 9 of 48 of the serum samples from the subjects did not exhibit bacteriostatic activities, especially the sera with the lowest concentrations of teicoplanin. Bactericidal activity was observed only when the teicoplanin concentrations were ≥20 mg/liter. Moreover, the bactericidal activity was generally low, with the activity more frequently being on the order of −1 and rarely on the order of −2 log changes in bacterial counts.

No adverse events, including hypersensitivity reactions and local site reactions, were reported in either group. Blood pressure measurements remained normal at all times, and orthostatic hypotension was not found. There were no significant abnormalities of the ECG parameters, including the QT segment, at the end of treatment. The results of tonal audiometry examinations remained normal for all volunteers. The biological parameters remained normal; however, the trend analysis showed a significant increase in alanine aminotransferase enzyme levels in group 2 (mean, median, and SD before treatment, 16.7, 15.0 and 7.0 IU/liter, respectively; mean, median, and SD at the end of treatment, 31.6, 28.5, and 15.4 IU/liter, respectively [P = 0.002, signed-rank test]). A decrease in the neutrophil count was also observed (mean, median, and SD before treatment, 4,672, 4,250, and 2,133/mm$^3$, respectively; mean, median, and SD at the end of treatment, 3,512, 3,324, and 1,061/mm$^3$, respectively [P < 0.02, signed-rank test]). As a decrease in the platelet count (mean, median, and SD before treatment, 220 × 10$^3$, 207 × 10$^3$, and 36 × 10$^3$/mm$^3$, respectively; mean, median, and SD at the end of treatment, 194 × 10$^3$, 188 × 10$^3$, and 36 × 10$^3$/mm$^3$, respectively [P < 0.02, signed-rank test]). For group 1 none of these trends were significant for these parameters except for the decrease in neutrophil count (mean, median, and SD before treatment, 3,965, 3,939, and 889/mm$^3$, respectively; mean, median, and SD at the end of treatment, 3,063, 3,432, and 1,117/mm$^3$, respectively [P < 0.02, signed-rank test]).
DISCUSSION

The results of this study show that the trough concentrations of teicoplanin in serum on day 11 of the alternate-day administration schedule (15 mg/kg administered every other day after loading doses of 12 mg/kg were administered three times every 12 h over days 1 and 2) are not inferior to the trough concentrations in serum obtained with a reference administration schedule (6 mg/kg administered daily after loading doses of 6 mg/kg were administered three times every 12 h over days 1 and 2).

The concentrations measured in plasma were in agreement with the concentrations predicted by the simulation according to the equation of Rowland (16), and for each subject the trough concentrations in serum exceeded 10 mg/liter at all time points, which was the target of the two treatments recommended in previous publications (12, 17).

Statistical analysis allowed us to conclude unequivocally with a small number of patients \( n = 24 \) the noninferiority of the group 2 treatment, although the SDs of the concentrations in serum in both groups (2.1 and 3.5 mg/liter in groups 1 and 2, respectively) were largely in excess of the value of 1 mg/liter assumed at the beginning of the study. This is due to the important differences observed between the groups.

The sera of healthy volunteers were constantly observed to

FIG. 2. Bactericidal activity of serum (change in the log concentration at 24 h from the concentration at time zero) against \( S. \) aureus strain 6017 (MIC, 4 mg/liter in MHB) as a function of the serum teicoplanin concentration measured in subjects in both groups.

FIG. 3. Bactericidal activity of serum (change in the log concentration at 24 h from the concentration at time zero) against \( S. \) aureus strain 1952 (MIC, 8 mg/liter in MHB) as a function of the serum teicoplanin concentration measured in subjects in both groups.
have bactericidal activities against all but one of the seven different Staphylococcus aureus strains tested. The teicoplanin MIC for one S. aureus strain was 8 mg/liter. Serum bactericidal activity was observed against this strain only when the measured teicoplanin concentration was ≥20 mg/liter. It is noteworthy that S. aureus strains for which MICs are 8 mg/liter are actually described to be of intermediate sensitivity, with sensitive strains being defined in France as those for which MICs are ≤4 mg/liter (13).

In contrast to those of Bailey et al. (1), the results of our study suggest that the bactericidal activity of teicoplanin in serum is in relation to the total teicoplanin concentration in serum. These findings correlate with the findings of Dykhuizen et al. (5), who showed that the sera of healthy volunteers receiving a single 200-mg dose of teicoplanin (as well as the sera of the same volunteers receiving a single 500-mg dose) was highly bactericidal against a strain of Streptococcus pyogenes and a strain of S. aureus (5). No bactericidal activity was found in the ultrafilter, and this may be due to the presence of teicoplanin at a concentration too low to produce bactericidal activity (however, the concentration was not measured), and the possibility that teicoplanin fixed to the dialysis membrane cannot be ruled out. As teicoplanin is typically 90% bound to serum proteins (between 88 and 94% according to Bernareggi et al. [2] and 97.4% according to Dykhuizen et al. over a concentration range of 1 to 11 mg/liter [5]), the results suggest that the protein-bound fraction of teicoplanin is also active.

The safety assessment was an important component of this study due to the use of high teicoplanin doses. No abnormalities in the results for any of the clinical or biological parameters measured, the ECG measures, or audiometric examination were observed. The data obtained in this study did not show evidence of nephrotoxicity or ototoxicity, although the biological parameters evaluated in this study might be considered relatively insensitive. A trend toward decreases in neutrophil and platelet counts was noted, as was a trend for an increase of alanine aminotransferase levels, although the levels always remained within the normal ranges. Although these findings only suggested trends, it should indicate the need for the use of caution in patients receiving high doses of teicoplanin. Of note is the experience of Graninger et al. (7), who treated patients with serious staphylococcal infections (osteomyelitis and endocarditis) with a mean loading dose of 15 mg/kg for 3 to 10 days in the hospital, followed by triweekly administration in an outpatient setting, with the doses subsequently adjusted to maintain a stable trough concentration in serum (approximately 10 mg/liter for patients with osteomyelitis and 20 mg/liter for patients with endocarditis). The mean dose was 15 mg/kg, with mean durations of treatment of 62 days for osteomyelitis and 49 days for endocarditis; three patients presented with thrombocytopenia, and one presented with leukopenia. These are already known adverse events, and caution is required for prolonged and/or high-dose treatments. All teicoplanin infusions (direct 1-min intravenous infusions) were very well tolerated. No clinical or clinically significant biological adverse events were reported by the subjects or observed by investigators, and no signs of hypersensitivity were noted.

The total dose of teicoplanin received was higher in group 2 (96 mg/kg) than in group 1 (66 mg/kg). Although this would generate higher costs for medication, the lower indirect costs related to administration on alternate days might compensate for these higher costs.

Conclusion. In conclusion, the alternate-day teicoplanin dosing schedule tested in this study (15 mg/kg on alternate days following administration of loading doses of 12 mg/kg three times every 12 h) could be considered an adequate alternative to the usually recommended regimen of 6 mg/kg daily. This mode of administration could be beneficial in clinically stable outpatients requiring treatment for long periods and could improve patient quality of life, which may improve compliance.

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REFERENCES