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Safety of high loading doses of teicoplanin: POSY-TEICO, a prospective, multicentre, observational study

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HIGHLIGHTS

- The POSY-TEICO study assessed the safety of HLD teicoplanin in a real-world setting.
- Incidence of nephrotoxicity with HLD of teicoplanin was determined
- Nephrotoxicity of HLD of teicoplanin was compared with historical data of vancomycin.
- Nephrotoxicity was 11.0% and 6.9% in loading and maintenance dose periods, respectively.
- Nephrotoxicity certainly/possibly related to teicoplanin was 12.4% in complete study period.

Journal Pre-proof

Safety of high loading doses of teicoplanin: POSY-TEICO, a prospective, multicentre, observational study

Running title: Incidence of nephrotoxicity in high teicoplanin dose

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Abstract

Background: Teicoplanin is used for treating infections caused by Gram-positive bacteria.

The POSY-TEICO study assessed the safety of a high loading dose (HLD) of teicoplanin (12 mg/kg twice daily) in a real-world setting.

Methods: This prospective study was conducted across six countries in Europe and enrolled adults prescribed HLD of teicoplanin between 2016–2019. The primary objective was to

determine the incidence of nephrotoxicity following HLD of teicoplanin over loading dose period. An independent clinical adjudication committee (ICAC) assessed all study outcomes related to nephrotoxicity.

Results: The study included 300 patients (males, 68.3%), with a mean age of 63.1 years and median teicoplanin treatment duration of 16 days (interquartile range: 9–38). Number of patients with bone and joint infection, infective endocarditis, and other severe infections was 176, 36, and 80, respectively. During loading dose period, 41 (13.8%) patients received 3 HLDs and 246 (82.8%) received ≥ 4 HLDs. Overall, 28 (11.0%) patients (95%CI, 7.4–15.5) experienced nephrotoxicity during loading and 10 (6.9%) patients (95%CI, 3.4–12.4) during maintenance dose periods. Number of patients who experienced nephrotoxicity certainly or possibly related to teicoplanin according to the ICAC was 20 (7.9%; 95%CI, 4.9–11.9), 8 (5.6%; 95%CI, 2.4–10.7) and 33 (12.4%; 95%CI, 8.7–16.9) across three study periods.

Conclusions: HLD of teicoplanin had an acceptable safety profile in patients treated for bone and joint infection, infective endocarditis, and other severe infections and no increased risk of nephrotoxicity was observed. However, patients should be closely monitored when HLDs are administered.

Keywords: Teicoplanin, safety, vancomycin, nephrotoxicity, Gram-positive bacteria, glycopeptide antibiotic,

1. Introduction

Teicoplanin, a glycopeptide antibiotic, is widely used in clinical practice for the treatment of infections caused by multidrug-resistant Gram-positive bacteria.[1] Teicoplanin has been marketed in Europe since 1988 and is approved for the parenteral treatment of the following infections: complicated skin and soft tissue infections, bone and joint infections, hospital-acquired pneumonia, community-acquired pneumonia, complicated urinary tract

infections, infective endocarditis, peritonitis associated with continuous ambulatory peritoneal dialysis, and bacteraemia that occurs in association with any of the above mentioned indications.[2] The risk of nephrotoxicity may be lower than that with glycopeptide vancomycin with potential additional advantages, including the possible use of other parenteral routes (intramuscular) and less frequent dosing due to its longer half-life. [3-6]

The dose and duration of teicoplanin treatment should be adjusted based on the type and severity of infection and the renal function of the patient. Since teicoplanin has a long elimination half-life, a steady-state concentration is only achieved after several days of treatment. To increase the chance of achieving a therapeutic trough serum concentration at Day 4, loading doses of teicoplanin are administered during the first days of treatment as teicoplanin follows area under the drug concentration–time curve / minimum inhibitory concentration dependent pharmacodynamics.[7-9] However, teicoplanin serum trough concentrations (C_{trough}) must be closely monitored when high doses are administered as overdoses are associated with a high risk of nephrotoxicity.[10] Following the loading dose regimen, teicoplanin should be administered according to a maintenance dose regimen. In adults with normal renal function, the loading dose varies between 6 and 12 mg/kg and should be given every 12 hours.[2] Yamada et al. suggested a loading dose of 6 mg/kg twice daily for three administrations for most infections and 12 mg/kg twice daily, hereafter referred to as ‘high loading doses’ (HLDs), for three to five administrations for difficult-to-treat infections, such as endocarditis and bone and joint infections.[11] The HLD of 12 mg/kg teicoplanin every 12 hours for three to five intravenous administrations is currently recommended for the treatment of infective endocarditis and bone and joint infections in the European harmonised summary of product characteristics (SmPC).[2] However, limited safety data are available for these HLD regimens.

Here we report results from the POSY (prospective, observational, safety study) -- TEICO Post-Authorization Safety Study (PASS), which assessed the incidence of nephrotoxicity in patients treated with high teicoplanin doses of 12 mg/kg twice daily in a real-world setting. The incidence rates observed with the HLD in this study were compared with previously reported rates of nephrotoxicity associated with high doses of vancomycin and lower loading doses of teicoplanin.

2. Methods

2.1 Study design and patients

The POSY-TEICO PASS was an observational, prospective, multicentre study (OBS13842) conducted in 32 centres across six countries in Europe (France, Germany, Italy, Poland, Romania, and United Kingdom) in patients infected with Gram-positive bacteria during 2016 and 2019.

The study included patients aged ≥ 18 years, with infection types for which the HLD of teicoplanin was approved (as per SmPC), who were prescribed teicoplanin loading doses of 12 mg/kg twice a day by the treating physician and who agreed to participate and sign the informed consent form (ICF). Patients with any history of hypersensitivity to teicoplanin or vancomycin were excluded. The treatment regimen was determined by the treating physician with reference to the SmPC. The study period was estimated around 2 years and 6 months.

The study duration for each patient included the loading dose period (up to 3 days), a maintenance dose analysis period (of variable duration depending upon the teicoplanin regimen of the individual patient) and a follow-up period of 60 days after the last administration of teicoplanin. Therapeutic monitoring of teicoplanin plasma concentration was left at the discretion of the physician in charge. To assess the incidence of nephrotoxicity and adverse events (AEs) following the HLD given in the first 3 days, the analysis of the

loading dose period extended up to Day 10 and the analysis of the maintenance period included data from Day 11 until teicoplanin discontinuation (**Figure 1**).

Protocol of the study is available on the website of the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP; [EUPAS12423](#)).

2.2 Assessments

The primary objective was to determine the incidence of nephrotoxicity reported in patients treated with HLD of teicoplanin (12 mg/kg twice daily) over the loading dose analysis period (up to Day 10). An independent clinical adjudication committee (ICAC) reviewed any potential cases of nephrotoxicity and adjudicated, which were considered confirmed cases of nephrotoxicity. Potential cases of nephrotoxicity were defined based on laboratory data showing an increase in serum creatinine of $>44.2\mu\text{mol/L}$ if the baseline serum creatinine was $\leq 265.2\mu\text{mol/L}$, or a rise of $>88.4\mu\text{mol/L}$ if the initial serum creatinine was $>265.2\mu\text{mol/L}$, or 50% increase from baseline or a drop in calculated creatinine clearance using Cockcroft-Gault formula of $\geq 50\%$ from baseline. Per the study protocol, the confirmed cases of nephrotoxicity were compared with external historical incidence rates of nephrotoxicity associated with vancomycin high dose [12-22] and with teicoplanin lower loading doses [23-27] from the literature data (**Supplementary Table S1 and S2**).

In a subsequent assessment, the ICAC reviewed the medical history of participants, including the prior and concomitant medications, to determine which confirmed cases of nephrotoxicity were considered certainly or possibly related to teicoplanin. A binary criterion (yes/no) was used to identify whether or not prior/concomitant medications received by these patients may have interfered with the occurrence of nephrotoxicity. Prior medications referred to those medications taken by the patient within 1 month prior to the first teicoplanin administration whereas concomitant medications were any treatment received by the patient from first teicoplanin administration up to the end of the study.

Secondary objectives included the incidence of nephrotoxicity during the maintenance and the entire study periods (adjudication by the ICAC as for the primary objective), the incidence of nephrotoxicity during all study periods based on either serum creatinine laboratory values or reported AEs (adjudication by the ICAC) and the incidence of hepatotoxicity, thrombocytopenia, hearing and balance/vestibular disorders, other renal events (renal failure, dialysis, and renal replacement therapy) and AEs during the loading dose, maintenance, and complete study periods. Renal failure (RF) was defined as rapid increase in serum creatinine over 150 $\mu\text{mol/L}$ or rapid decrease in creatinine clearance below 50 mL/min. Hepatotoxicity was defined as aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≥ 3 times upper limit of normal (when AST or ALT was normal or missing at baseline) or, if AST or ALT baseline was abnormal, AST or ALT increase of ≥ 3 times the baseline; and/or AEs/reactions using the standardised Medical Dictionary for Regulatory Activities (MedDRA) query for (SMQ) 'Hepatic Disorders'. Incidence of thrombocytopenia was reported as platelets $< 100,000/\text{mm}^3$. Hearing disorder was identified via preferred term (PT) terms using the MedDRA SMQ for 'Hearing and vestibular disorders' (narrow) and additionally the PT 'balance disorder'.

2.3 Analysis population

The primary analysis population was the modified high dose-treated population. This consisted of patients who were exposed to ≥ 3 HLDs of teicoplanin, with at least 2 injections within 24 hours, a first dose of > 10 mg/kg and a cumulative dose of ≥ 20 mg/kg within 30 hours. The analysis of secondary endpoints including AE data was done on the safety population. The safety population consisted of patients who were exposed to at least one dose of teicoplanin. Overdose was defined as having had at least one AE reported as "overdose" (with Medical Dictionary for Regulatory Activities [MedDRA] PT containing the word

“overdose”); and/or having received ≥ 6 HLDs and/or having received at least one dose >13 mg/kg.

2.4 Statistical analysis

The primary analysis was descriptive, and the incidence of nephrotoxicity over the loading dose analysis period (up to Day 10) was computed with exact binomial 95% confidence interval (CI). Multiple occurrences of nephrotoxicity in the same patient were counted only once (first occurrence considered only). A sample size of 300 patients was calculated based on the expected incidence of nephrotoxicity (primary evaluation criteria). A systematic literature search was conducted to identify studies from Embase and Medline databases published during a period of January 1995 till December 2014. Search terms included “vancomycin” in combination with “nephrotoxicity” or “renal toxicity” or “renal injury.” Studies written in languages other than English and those presented solely as abstracts or posters at scientific conferences were not considered in this literature review. This systematic literature search identified twelve studies (**Supplementary Table S1**) which were included in the meta-analysis using random effects model for the calculation of the reference incidence and a test of homogeneity was performed. [12-22] Forest plot of events denoting nephrotoxicity associated with vancomycin high dose is presented in **Supplementary Figure S1**. The expected incidence of nephrotoxicity associated with high doses of vancomycin ($C_{\text{trough}} \geq 15$ mg/L) varied between 6.9% and 55.1%. [12-22] The incidence of nephrotoxicity associated with high dose of vancomycin was estimated to be about 22%. Nephrotoxicity with HLD teicoplanin should not exceed the historical reference incidence of vancomycin by $>5\%$ (i.e., non-inferiority [NI] margin). Hence, the upper limit of 95% two-sided CI of the observed incidence with HLD teicoplanin should be $<27\%$ (historical reference incidence + NI margin: $22 + 5$), to evaluate NI versus vancomycin. Assuming a slightly better true incidence of 20% under teicoplanin, a sample size of 300 patients provided 80% power to

evaluate the NI. Similarly, another systematic literature search was conducted to identify studies reporting incidence of nephrotoxicity associated with a lower loading dose of teicoplanin from Embase and Medline databases published during a period of January 1990 till December 2014. This systematic literature search identified five studies (**Supplementary Table S2**) which were included in the meta-analysis performed using fixed effects model. [23-27] Forest plot of events denoting nephrotoxicity associated with lower loading dose of teicoplanin is presented in **Supplementary Figure S2**. The incidence of nephrotoxicity associated with lower loading dose of teicoplanin was estimated to be about 2%.

Secondary analyses were mainly descriptive and consisted of incidence rates and associated 95% CI. Multivariate analysis to identify potential predictive factors for nephrotoxicity, hepatotoxicity, thrombocytopenia, and hearing and balance disorders were exploratory. A stepwise multivariate logistic regression model was built from variables significant at the 20% level at previous univariate step until no further candidate variables could enter in the model at the 5% significance level. The adjusted odds ratio and their 95% CI were provided for the variables finally selected in the model.

For time to event analysis, missing data were handled based on censoring rules. Patients who were lost to follow-up for survival data were considered censored at the last observation. For categorical data, missing data were reported as missing. In case the missing data concerned with the primary objective assessment, the patient could be considered having an insufficient post-administration follow-up (e.g., missing laboratory data: serum creatinine, creatinine clearance). For the primary evaluation criterion, a sensitivity analysis related to missing data was also performed. The assumption was made that, for the missing data, the incidence of nephrotoxicity varied between half and twice the incidence observed (the observed rate in non-missing data was applied to the patients with missing data, with this rate

divided by two in a first scenario (sensitivity 1) and multiplied by two in a second scenario (sensitivity 2)).

2.5 Ethics

The institutional review board or independent ethics committee of each centre approved the study (approval numbers are listed in **Supplementary Table S3**). This study followed the principles of the Declaration of Helsinki and the Good Clinical Practice Guidelines of the International Conference on Harmonization. All patients provided written informed consent. The protocol of the study was approved by the European Medicines Agency and was registered in the European Union electronic Register of Post-Authorization Studies (EUPAS12423) prior to the start of the study.

3. Results

3.1 Baseline characteristics

A total of 300 patients (205 males, 68.3%) with a mean (SD) age of 63.1 (15.0) years were enrolled in the study and received at least one dose of teicoplanin (safety population).

Baseline and disease characteristics are presented in **Table 1**. Number of patients as teicoplanin indication with bone and joint infections, infective endocarditis, other severe infections (sepsis, mediastinitis, urinary tract infection, abdominal enterococcus infection, cellulitis, etc.) were 176, 36 and 80, respectively. Proportion of patients with chronic kidney disease (CKD) / RF / renal impairment (RI) / nephropathy / under dialysis at baseline was 9.7% (n=29). Baseline renal function data has been added in the **Supplementary Table S4**. In total, 282 (94.0%) patients had received prior medications within one month to inclusion, and 295 (98.3%) patients received at least one concomitant medication.

3.2 Patient disposition

Of 300 patients, 205 (68.3%) completed their teicoplanin treatment. Of the 95 (31.7%) patients who did not complete their treatment, 46 discontinued due to AEs, 16 due to lack of efficacy and 33 for other reasons (**Supplementary Table S5**).

3.3 Treatment exposure

The median duration of teicoplanin treatment was 16 days (interquartile range [IQR: 9–38]). Out of the 300 patients treated with teicoplanin, 287 (95.7%) received ≥ 3 HLDs (modified high-dose-treated population). During the loading dose period, 41 (13.8%) patients received 3 HLDs, 70 (23.6%) received 4 HLDs, 54 (18.2%) received 5 HLDs, 49 (16.5%) received 6 HLDs, 24 (8.1%) received 7 HLDs, 24 (8.1%) received 8 HLDs and 25 (8.4%) received ≥ 9 HLDs. The mean (SD) teicoplanin dose was 11.1 (1.8) mg/kg during the loading dose period, 10.3 (3.7) mg/kg during the maintenance dose period and 10.8 (2.6) mg/kg during the complete study period. Overall, 164 (54.7%) patients had an overdose of teicoplanin: 133 patients (44.3%) had at least 6 HLDs of teicoplanin, 48 patients (16.0%) had at least one dose of teicoplanin superior to 13 mg/kg, and 22 patients (7.3%) had an AE ‘overdose’ (one patient could present several of these 3 categories). Forty-five (15%) patients were administered teicoplanin subcutaneously (SC) (off-label use) during the study. In the loading dose analysis period, 33 (22%) patients received teicoplanin SC.

3.4 Nephrotoxicity during the loading dose period (primary objective)

In the modified high-dose-treated population, 255 of 287 patients were evaluable for nephrotoxicity over the loading dose period. Of these, 28 (11.0%; 95% CI, 7.4–15.5) patients experienced nephrotoxicity confirmed by the ICAC (**Table 2**). The HLD of teicoplanin was non-inferior to vancomycin as the upper limit of the 95% CI of 15.5% was lower than 27% (the NI margin versus vancomycin). Consistent results were also observed in the safety population and in both sensitivity analyses (sensitivity 1: missing data considered as half of the observed frequency; sensitivity 2: missing data considered as twice the observed

frequency) (**Table 2**). When compared with lower doses of teicoplanin, the lower limit of the 95% CI of 7.4%, was above the estimated incidence associated with the lower loading dose of teicoplanin, which was >2%.

3.5 Nephrotoxicity during the maintenance and complete study periods

Overall, 10 (6.9%) of 144 evaluable patients during the maintenance dose analysis period and 56 (20.7%) of 271 evaluable patients during the complete study period presented nephrotoxicity, as confirmed by the ICAC (**Table 2**).

3.6 Nephrotoxicity classified as related to teicoplanin

Overall, 20 (7.9%) of 253, 8 (5.6%) of 144 and 33 (12.4%) of 267 evaluable patients during the loading, maintenance, and complete study periods, respectively, experienced nephrotoxicity certainly or possibly related to teicoplanin according to the ICAC (**Table 2**).

3.7 Nephrotoxicity based on laboratory values and reported AEs

Of the 300 patients in the safety population, 55 patients presented an event of potential nephrotoxicity according to laboratory criteria and 66 patients presented an event classified as a potential sign of nephrotoxicity based on predefined MedDRA PTs (e.g., acute kidney injury, blood creatinine increased, hyponatraemia, CKD, RF, hyperkalaemia, toxic nephropathy, and renal impairment). Of the 66 patients with an AE, 64 patients had an underlying disease with a known risk of nephrotoxicity (including sepsis or bacteraemia, diabetes, kidney, cardiovascular comorbidity, hypertension, or peripheral vascular disorders) and 65 patients had multiple concomitant or prior medications with a known risk of nephrotoxicity. Medications used included nonsteroidal anti-inflammatory drugs and paracetamol (81.8%), proton pump inhibitors (69.7%), aminoglycosides (54.5%), furosemide (50.0%), penicillin (42.4%), anaesthetic agents and cephalosporins (each 33.3%), ciprofloxacin and other fluoroquinolones (30.3%), vancomycin and rifampicin (each 28.8%), angiotensin-converting-enzyme inhibitors (27.3%), angiotensin receptor blockers (13.6%),

thiazide diuretics (13.3%), norepinephrine/phenylephrine HCl and allopurinol (each 11.7%), amphotericin B (10.0%), and phenytoin (1.5%).

Following a review by the ICAC, in the complete study period, 58 (20.6%) of 282 patients had confirmed nephrotoxicity and 34 (12.2%) of 278 patients had a confirmed nephrotoxicity considered certainly or possibly related to teicoplanin (**Table 2**). In the loading dose period, 30 (11.3%) of 265 patients had confirmed nephrotoxicity and 21 (8.0%) of 263 patients had a confirmed nephrotoxicity certainly or possibly related to teicoplanin (**Table 2**). In the loading dose period, the mean (SD) teicoplanin C_{trough} was 32.85 (9.97) mg/L; (IQR; 26-37.6) in patients with confirmed nephrotoxicity and 27.88 (9.26) mg/L; (IQR; 21.9-34.2) in patients without nephrotoxicity.

For the complete study period, the rate of nephrotoxicity confirmed by the ICAC was 27.6% (43/156) for patients with an overdose versus 11.9% (15/126) for patients with no overdose, 21.2% (44/208) for infective endocarditis (IE) or bone and joint infection (BJI) versus 18.9% (14/74) for other severe infections, and 28.6% (12/42) for patients administered SC teicoplanin (off-label) versus 19.2% (46/240) for patients administered intramuscular or intravenous teicoplanin. The incidence of nephrotoxicity separating BJI and IE for modified high-dose treated population and safety population has been added in the **Supplementary Table S6**.

On multivariate analysis, predictive factors for nephrotoxicity were the cumulative doses of HLD of teicoplanin, prior peripheral vascular disorder (ongoing) and low creatinine clearance at baseline.

3.8 Hepatotoxicity, thrombocytopenia, hearing and balance/vestibular disorders

The proportion of patients who experienced hepatotoxicity, hearing and balance/vestibular disorder and thrombocytopenia was 18/205 (8.8%), 10/127 (7.9%) and 37/287 (12.9%) during the loading 2/287 (0.7%), 3/196 (1.5%) and 6/287 (2.1%) during the maintenance and

18/261 (6.9%), 6/151 (4.0%) and 32/281 (11.4%) during the complete study periods, respectively. Among the 32 patients with thrombocytopenia, 10 had a baseline platelets value $<100,000/\text{mm}^3$.

Potential predictive factors for hepatotoxicity were high body mass index, hypotension, and liver disorders. Potential predictive factors for thrombocytopenia were hypovolemic shock, liver disorder, CKD, and haematological malignancy (all prior, ongoing). No predictive factors for hearing and balance/vestibular disorders were identified.

3.9 Other adverse events

Potentially clinically significant abnormalities are presented for creatinine and urea in **Table 3**. No new signal was found while examining these data. Of 300 patients in the safety population, 235 (78.3%) patients experienced ≥ 1 treatment-emergent AE (TEAE), 96 (32.0%) experienced ≥ 1 TEAE related to teicoplanin, 124 (41.3%) experienced ≥ 1 serious AE (including 19 [6.3%] related to teicoplanin), and 31 (10.3%) patients died. The death of one (0.3%) patient with serious AEs of eosinophilia (not related to teicoplanin), hypoxic-ischaemic encephalopathy (not related to teicoplanin) and acute kidney injury (possibly related to teicoplanin) was adjudicated as possibly related to teicoplanin according to the ICAC. The summary of TEAEs is presented in **Supplementary Table S7**.

4. Discussion

This study included patients with Gram-positive infection treated with HLD of teicoplanin (12 mg/kg twice daily) in a real-world setting. The rate of nephrotoxicity in patients, confirmed by the ICAC, was 11.0% during the loading dose analysis period in the primary analysis population (modified HLD population); the upper limit of the 95% CI was 15.5%, which was less than 27% (NI margin versus vancomycin). Overall, 20/253 (7.9%) patients during the HLD period, 8/144 (5.6%) patients during the maintenance period and 33/267

(12.4%) patients during the complete study period experienced nephrotoxicity, which was certainly or possibly related to teicoplanin according to the ICAC.

The lower limit of the 95% CI (7.4%) during the loading dose period in the modified HLD population was above the estimated incidence associated with the lower loading dose of teicoplanin, which was 2%. Results were also consistent in the safety population and for both sensitivity analyses.

The proportion of patients with hepatotoxicity, thrombocytopenia, hearing and balance/vestibular disorders, additional renal endpoints and any AEs did not raise any new safety concerns for this cohort of patients with severe infections, treated with HLD of teicoplanin.

In the current study, 66 patients experienced nephrotoxicity as an AE during the complete study period. Of them, 64 had an underlying disease (including sepsis or bacteraemia, diabetes, kidney, or cardiovascular comorbidity) and 65 patients had multiple concomitant or prior medications with known risk of nephrotoxicity. This finding is in alignment with the fact that nephrotoxicity can be associated with multiple other risk factors, such as comorbidities and concomitant medications. Amongst these 66 patients, 45 cases were related to overdose (68.2%) and 13 cases (19.7%) related to the use for other severe infections. Among these cases, the top 5 risk factors to nephrotoxicity from medical history/concurrent conditions/underlying diseases included sepsis or bacteraemia, diabetes, underlying renal diseases, cardiac failure, and hypertension; while the top 5 risk factors from concomitant or previous medications include NSAIDs, PPI, aminoglycosides, furosemide, and Penicillin's.

This study had some limitations. The primary analysis was descriptive and for the evaluations versus external historical reference (high dose of vancomycin) and lower loading dose of teicoplanin, precise person-days exposures to vancomycin and/or teicoplanin were

not available in the published literature; therefore, the incidence rates have been calculated using the mean or median duration of treatment and provided an approximate estimate of the incidence rate. Also, due to heterogeneity across the patient populations in external historical reference, an analysis using a random-effects model along with a test of homogeneity was conducted to pool the estimates from the historical data. This study had some strengths for limiting bias. All data specific to the research question and objectives were prospectively collected and recorded in a consistent way for each patient. The participating physicians assessed the treatment with teicoplanin as per routine clinical practice. The data collected were monitored while the study was being conducted enabling a continuous evaluation of safety of teicoplanin.

In conclusion, in this real-world study in patients treated for bone and joint infection, infective endocarditis, or other severe infections, HLD (12 mg/kg twice daily) of teicoplanin had an acceptable safety profile and was not related with an increased risk of nephrotoxicity compared with historical data of high-dose vancomycin. However, patients should be closely monitored when HLDs of teicoplanin are administered.

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Declarations

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Competing Interests: MKA was an employee of Sanofi at the time of the study and may hold shares and/or stock options in the company. RG, NT, FP, and PT have no conflict of interest to declare.

Ethical Approval: The institutional review board or independent ethics committee. Approval numbers are listed in Supplementary Table S1

Sequence Information: Not applicable

Author contributions

Conception and design of the study: Remy Gauzit

Contributions to data collection: Rémy Gauzit, Naomi Thompson, Federico Pea, and Pierre Tattevin

Contributions to data analysis: Marmar Kabir-Ahmadi

Contributions to data interpretation: Rémy Gauzit, Marmar Kabir-Ahmadi, Naomi Thompson, Federico Pea, and Pierre Tattevin

Contributions to manuscript writing: All authors critically reviewed manuscript drafts and approved the final version for submission. All authors are responsible for the work described in this paper. All authors had full access to the data and agreed to be accountable for the for the integrity of the data and the accuracy of the data analysis.

Figure Legend

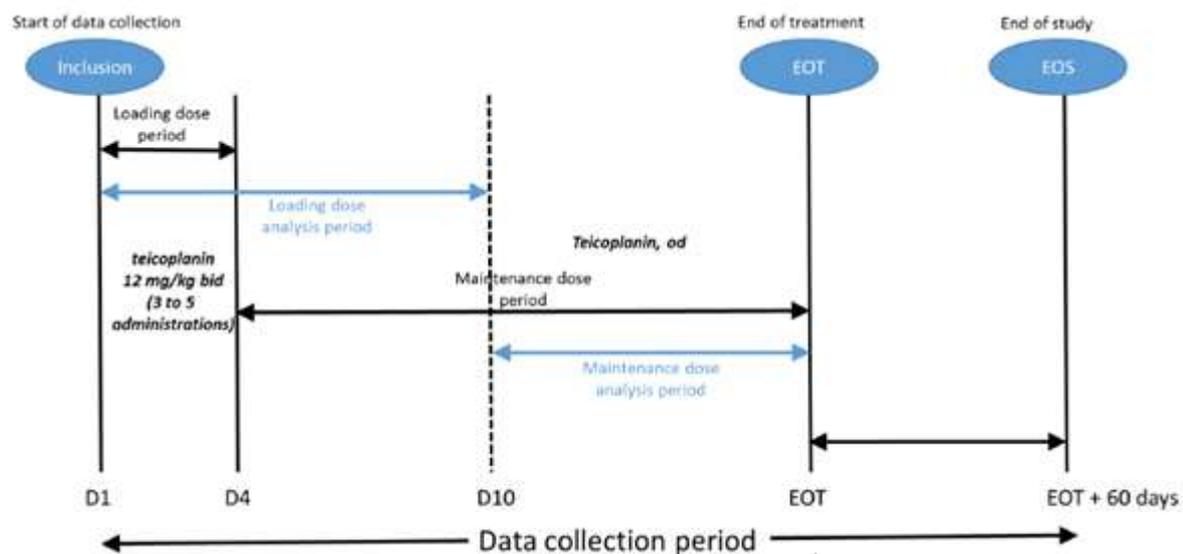


Figure 1. Study design

The duration of the loading dose period was defined based on teicoplanin SmPC recommendation for the 12 mg/kg BID, i.e., 3 to 5 administrations for severe infections such as endocarditis, bone, and joint infections. The duration of the maintenance dose period depended upon completion of the planned teicoplanin regimen duration for each individual patient. The duration of the follow-up period was defined as 60 days after the last administration of teicoplanin.

BID, twice daily; D, day; EOS, end of study; EOT, end of treatment.

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Table 1. Baseline demographics and disease characteristics

| | Enrolled patients (safety population) |
|---|--|
| | <i>N</i> = 300 |
| Age (years), mean (SD) | 63.1 (15.0) |
| Male, <i>n</i> (%) | 205 (68.3) |
| Weight (kg) ^a , mean (SD) | 81.64 (20.71) |
| BMI (kg/m ²) ^b , median (Q1–Q3) | 26.93 (23.53–31.18) |
| Heart rate (beats/min) ^b , median (Q1–Q3) | 80.0 (70.0–89.0) |
| Body Temperature (°C) ^b , median (Q1–Q3) | 36.8 (36.0–37.0) |
| Diastolic Blood Pressure (mmHg) ^c , median (Q1–Q3) | 70.0 (60.0–77.0) |
| Systolic Blood Pressure ^c (mmHg), median (Q1–Q3) | 122.0 (110.0–137.0) |
| Teicoplanin indication, <i>n</i> (%) | |
| Bone and joint infections | 176 (58.7%) |

| | |
|--|------------------|
| Infective endocarditis | 36 (12.0%) |
| Other severe infection | 80 (26.7%) |
| Glasgow coma scale, median (Q1–Q3) | 15.0 (15.0–15.0) |
| Under Medical history / underlying disease, <i>n</i> (%) | |
| Sepsis / bacteraemia | 33 (11%) |
| Diabetes | 30 (10%) |
| CKD / RF / RI / nephropathy / under dialysis | 29 (9.7%) |
| Cardiac failure | 26 (8.7%) |
| Hypertension | 26 (8.7%) |
| Peripheral vascular disorders with other risk factors ^d | 24 (8%) |

BMI, body mass index; CKD, chronic kidney disease; Q, quartile; RF, renal failure; RI, renal impairment; SD, standard deviation

Overall number of patients varied for a few parameters; overall patient numbers have been described with parameters.

^aMissing value for two patients.

^bMissing values for five patients.

^cMissing values for three patients.

^dRisk factors from either medical history or concomitant medications, the latter ones were hypotension/hypovolaemia/shock, hypoalbuminaemia, liver disorder, tobacco user, dyslipidemia, obesity, alcoholism/alcohol use/alcohol withdrawal syndrome.

Table 2. Cases of confirmed nephrotoxicity as per adjudication by the ICAC

| | High Loading dose period | Maintenance dose period | Complete study period |
|--|-----------------------------|----------------------------|--------------------------|
| Modified high-dose treated population | <i>N</i> = 287 | <i>N</i> = 196 | <i>N</i> = 287 |

| | | | |
|--|-----------------------|-----------------------|-----------------------|
| Nephrotoxicity (ICAC validation), <i>n</i> | 255 | 144 | 271 |
| <i>n</i> (%) | 28 (11.0) | 10 (6.9) | 56 (20.7) |
| 95% CI | 7.4–15.5 | 3.4–12.4 | 16.0–26.0 |
| <hr/> | | | |
| Certainly or possibly related to teicoplanin according to ICAC, <i>n</i> | 253 | 144 | 267 |
| <i>n</i> (%) | 20 (7.9) | 8 (5.6) | 33 (12.4) |
| 95% CI | 4.9–11.9 | 2.4–10.7 | 8.7–16.9 |
| <hr/> | | | |
| Sensitivity analysis, <i>n</i> | 287 | 196 | 287 |
| Sensitivity 1, <i>n</i> (%) | 29 (10.1) | 12 (6.1) | 57 (19.9) |
| 95% CI | 6.9–14.2 | 3.2–10.5 | 15.4–25.0 |
| Sensitivity 2, <i>n</i> (%) | 35 (12.2) | 17 (8.7) | 62 (21.6) |
| 95% CI | 8.7–16.6 | 5.1–13.5 | 17.0–26.8 |
| <hr/> | | | |
| Safety population | <i>N</i> = 300 | <i>N</i> = 202 | <i>N</i> = 300 |
| <hr/> | | | |
| Confirmed nephrotoxicity, <i>n</i> | 265 | 149 | 282 |
| <i>n</i> (%) | 30 (11.3) | 10 (6.7) | 58 (20.6) |
| 95% CI | 7.8–15.8 | 3.3–12.0 | 16.0–25.8 |
| <hr/> | | | |
| Certainly or possibly related to teicoplanin, <i>n</i> | 263 | 149 | 278 |
| <i>n</i> (%) | 21 (8.0) | 8 (5.4) | 34 (12.2) |
| 95% CI | 5.0–11.9 | 2.4–10.3 | 8.6–16.7 |
| Bone and Joint infection and infective endocarditis, <i>n</i> | 192 | 124 | 208 |
| <i>n</i> (%) | 24 (12.5) | 9 (7.3) | 44 (21.2) |

95% CI

8.2-18.0

3.4-13.3

15.8-27.3

AE, adverse event; CI, confidence interval; ICAC, independent clinical adjudication committee; *N*, total number of patients; *n*, number of evaluable patients or number of responders

Table 3. Renal function (safety population)

| Parameter | Baseline | PCSA criteria | High Loading dose period | Maintenance dose period | Complete study period |
|----------------------------|----------------|----------------------------|--------------------------|-------------------------|-----------------------|
| Creatinine (µmol/L) | Overall | ≥150 | 43/276 | 23/156 | 46/289 |
| | | µmol/L | (15.6%) | (14.7%) | (15.9%) |
| | | ≥30% change from baseline | 33/276 | 24/156 | 44/289 |
| | | (12.0%) | (15.4%) | (15.2%) | |
| | | ≥100% change from baseline | 9/276 | 7/156 | 14/289 |
| | (3.3%) | (4.5%) | (4.8%) | | |
| | Normal/missing | ≥150 | 19/245 | 8/137 | 21/258 |
| | | µmol/L | (7.8%) | (5.8%) | (8.1%) |
| | | ≥30% change from baseline | 30/245 | 23/137 | 41/258 |
| | | (12.2%) | (16.8%) | (15.9%) | |
| ≥100% change from baseline | | 7/245 | 5/137 | 11/258 | |
| (2.9%) | (3.6%) | (4.3%) | | | |

| | | | | | | |
|------------------|--------------------|------------------------------|---|-------------------|-------------------|-------------------|
| | | ≥ 150 $\mu\text{mol/L}$ | ≥ 150 | 24/31 (77.4%) | 15/19 (78.9%) | 25/31 (80.6%) |
| | | | $\geq 30\%$ change from baseline | 3/31 (9.7%) | 1/19 (5.3%) | 3/31 (9.7%) |
| | | | $\geq 100\%$ change from baseline | 2/31 (6.5%) | 2/19 (10.5%) | 3/31 (9.7%) |
| Urea (mmol/L) | Overall | ≥ 17 mmol/L | ≥ 17 mmol/L | 32/263 (12.2%) | 19/146 (13.0%) | 42/281 (14.9%) |
| | Normal/ missing | ≥ 17 mmol/L | ≥ 17 mmol/L | 16/243 (6.6%) | 12/137 (8.8%) | 22/260 (8.5%) |
| | | ≥ 17 mmol/L | ≥ 17 mmol/L | 16/20 (80.0%) | 7/9 (77.8%) | 20/21 (95.2%) |

PCSA, potentially clinically significant abnormalities.