Clinical Pharmacokinetics (2024) 63:1271–1282
https://doi.org/10.1007/s40262-024-01410-2

ORIGINAL RESEARCH ARTICLE

Population Pharmacokinetics and Pharmacodynamics of Dalbavancin and C-Reactive Protein in Patients with Staphylococcal Osteoarticular Infections

Pier Giorgio Cojutti[1,2] · Sara Tedeschi[1,3] · Eleonora Zamparini[3] · Pierluigi Viale[1,3] · Federico Pea[1,2]

Accepted: 9 August 2024 / Published online: 22 August 2024

Abstract

Background and Objective Dalbavancin is increasingly used for the long-term treatment of chronic osteoarticular infections. A population pharmacokinetic/pharmacodynamic (PK/PD) analysis for assessing the relationship between dalbavancin exposure and C-reactive protein (C-RP) over time was conducted.

Methods Non-linear mixed-effect modeling was fitted to dalbavancin and C-RP concentrations. Monte Carlo simulations assessed the weekly percentage of C-RP reduction associated with different dosing regimens, starting from baseline to < 1 mg/dL.

Results A total of 45 patients were retrospectively included in the analysis. The PK of dalbavancin was described by a two-compartment model, and the PD of C-RP was described by an indirect turnover maximum inhibition model. The total dalbavancin concentration model estimate producing 50% of maximum C-RP production inhibition (IC_{50}) was 0.70 mg/L. Monte Carlo simulations showed that in patients with staphylococcal osteoarticular infections targeting total dalbavancin concentrations at > 14.5 mg/L at any time point may achieve C-RP production inhibition over time in > 95% of patients. Based on this, the findings showed that a cumulative dose of 3000 mg administered in the first 3 weeks may lead to a > 90% C-RP decrease versus baseline in approximately 5–6 weeks. In patients needing treatment prolongation, an additional 1500 mg dose after this period may maintain C-RP concentrations < 1 mg/dL for other 3 weeks.

Conclusions A decrease in C-RP is related to dalbavancin exposure in osteoarticular infections. Targeting dalbavancin plasma concentrations above the efficacy threshold may be associated with effective treatment.

1 Introduction

Dalbavancin is a new lipoglycopeptide antibiotic highly active against multidrug-resistant Gram-positive staphylococci, including methicillin-resistant *Staphylococcus aureus* (MRSA) [1, 2].

Key Points

A model describing the population pharmacokinetics and pharmacodynamics of dalbavancin and C-reactive protein (C-RP) in osteoarticular infections was developed using real-world clinical data.

Targeting total dalbavancin plasma concentrations > 14.5 mg/L at any timepoint during treatment may achieve C-RP production inhibition in > 95% of patients.

Monte Carlo simulation showed that a cumulative dalbavancin dose of 3000 mg in the first 3 weeks may lead to a > 90% C-RP reduction within 5–6 weeks.

✉ Pier Giorgio Cojutti
piergiorgio.cojutti@unibo.it

1 Department of Medical and Surgical Sciences, Alma Mater Studiorum, University of Bologna, Bologna, Italy

2 Clinical Pharmacology Unit, Department for Integrated Infectious Risk Management, IRCCS Azienda Ospedaliero-Universitaria di Bologna, 40138 Bologna, Italy

3 Infectious Diseases Unit, Department for Integrated Infectious Risk Management, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy

Dalbavancin is currently approved for the treatment of acute bacterial skin and skin structure infections (aBSSSI); however, thanks to its long elimination half-life, a good tissue diffusion that makes this drug a reliable treatment option for deep-seated infection, and a remarkable antibiofilm activity [3, 4], dalbavancin use has been extended to the long-term treatment of several subacute and/or chronic infections [5]. In this regard, dalbavancin may represent a valuable option for treating MRSA-related bone and joint infections, namely prosthetic joint infections, osteomyelitis and spondylodiscitis [6, 7]. In these clinical scenarios, treatment duration should last from a minimum of 4 weeks up to several months, depending on the patient case-mix complexity [8–11]. Noteworthy, long-acting antibiotics such as dalbavancin may offer an opportunity of simplifying therapeutic management after hospital discharge, also thanks to a better safety profile compared with other anti-MRSA agents (i.e. vancomycin, linezolid or daptomycin) [12].

Dalbavancin is administered by the intravenous route, has extensive plasma protein binding (93–98%), has a terminal half-life of 147–258 h, and up to 42% of the administered dose is excreted in urine. Dalbavancin is not a substrate of the hepatic cytochromes and has no clinically relevant drug–drug interactions [13].

In a neutropenic murine thigh infection model, it was shown that a dalbavancin free daily area under the concentration-time curve ($fAUC_{24}$)/minimum inhibitory concentration (MIC) ratio > 111.1 was associated with a 2-log kill against *Staphylococcus aureus* isolates [14]. Based on this assumption, by taking care of the finding of an almost linear relationship existing between dalbavancin AUC_{24} and total plasma concentration at any time point in patients receiving dalbavancin treatment, our group proposed that therapeutic drug monitoring (TDM) could represent a valuable approach for dealing with long-term dalbavancin treatment. Briefly, it was shown that maintaining total plasma dalbavancin concentration above the threshold of 4.02 or 8.04 mg/L should grant appropriate efficacy over time, in terms of ensuring an $fAUC_{24}$/MIC ratio > 111.1, against staphylococci with an MIC up to MIC_{90}, that is the value at which 90% of the wild-type strains are inhibited (namely 0.0625 mg/L), or to the EUCAST clinical breakpoint (namely 0.125 mg/L), respectively [15].

Based on this PK/PD target attainment, in a recent survey and opinion article involving experts from different European countries, it was suggested that administering an overall dalbavancin dosing regimen of 3000 mg over the first 3 weeks of treatment should grant appropriate efficacy for up to 4–6 weeks, irrespective of the three different administration schemes chosen (namely, 1500 mg on days 1 and 8, 1500 mg on days 1 and 15, or 1500 mg on day 1 and 500 mg on days 8, 15 and 22) [16]. However, it was agreed that whenever treatment duration should last longer than 6 weeks, TDM of dalbavancin should be highly recommended [16].

This latter occurrence could be the case in the specific scenario of bone and joint infections, in which treatment duration extent might vary greatly depending on both the clinical response, in terms of improvement/resolution of the infectious signs and symptoms, and the dynamics over time of an inflammatory biomarker such as C-reactive protein (C-RP) [8–11]. Consequently, creating a pharmacokinetic/pharmacodynamic (PK/PD) model that is useful at predicting the relationship existing between dalbavancin exposure and C-RP production inhibition over time may be helpful for clinicians in better understanding patient response to treatment.

The aim of this study was to conduct a population PK/PD analysis of the relationship between dalbavancin exposure and C-RP over time in patients receiving long-term treatment with dalbavancin because of documented or suspected staphylococcal osteoarticular infections.

2 Methods

2.1 Study Design

This retrospective study was conducted at the IRCCS, Azienda Ospedaliero-Universitaria di Bologna, Italy, during the period January 2021–August 2023, among patients having documented or suspected staphylococcal osteoarticular infections treated with dalbavancin monotherapy after completing an initial 2-week in-hospital daptomycin-based combination therapy. The study was approved by the local Ethics Committee (registration number 897/2021/Oss/AOUBo), and, according to hospital policies, signed informed consent was waived due to the retrospective observational design of the investigation.

All patients had an initial dalbavancin dosing regimen based on two 1500 mg doses 1 week apart (on days 1 and 8), and underwent TDM after at least 21 days from the start of treatment, as suggested in a previous study [5]. Briefly, the first TDM assessment should be performed in the time interval between 21 and 35 days, depending on the patient's renal function, in order to be sure of maintaining, over time, dalbavancin plasma concentrations above the efficacy threshold. Dalbavancin total plasma concentrations were measured by means of a validated liquid chromatography-tandem mass spectrometry method as previously described [17]. The intra- and interday coefficients of variation of quality controls were 9.0–14.0% and 4.8–14.2%, respectively. The lower limit of quantification was 0.5 mg/L. A persisting total dalbavancin plasma concentration ≥ 8.04 mg/L was considered adequate for efficacy, as it may grant an $fAUC_{24}$/MIC ratio

> 111.1 against staphylococci, with an MIC value up to the EUCAST clinical breakpoint, as previously described [15]. TDM reassessments were subsequently performed whenever feasible, and additional TDM-guided dalbavancin doses were administered whenever clinically needed on a case-by-case basis. C-RP levels were assessed at baseline, i.e. at the first dalbavancin administration and at each TDM instance.

Model-informed precision dosing (MIPD) was used by means of a TDM-based Bayesian method (developed with MwPharm++ software – Mediware®) for forecasting the duration of exposure ≥ 8.04 mg/L and the eventual need for re-dosing, as previously described [18]. Clinical pharmacological advice on when to administer the next dose was then provided to clinicians. TDM-based MIPD was performed for all TDM samples, as long as a patient was treated with dalbavancin. In MIPD, TDM data along with demographic and clinical information (age, height, weight, sex, estimated glomerular filtration rate [eGFR]) were used to calculate individual dalbavancin PK parameters. The *a posteriori* approach was used for estimating the duration of effective exposure and for anticipating the best timing for eventual re-dosing [18].

This approach is particularly helpful for patients requiring long-term treatments and in the extremes of renal function. In fact, even if dalbavancin dose should be reduced in patients with impaired renal function as per the summary of product characteristics, when more than two doses are needed there are no specific indications on how to modify drug dose according to varying renal function.

Only those patients fulfilling the following inclusion criteria were selected for analysis: diagnosis of bone and joint infections, previous antimicrobial treatment with a daptomycin-based combination regimen, availability of at least two C-RP concentrations, of which one was available at the start of dalbavancin treatment for assessing the C-RP baseline value.

Patient data retrieved from clinical records included demographics (age, weight, height, sex), clinical data (type and site of infection, previous antibiotic regimens) and laboratory data (serum creatinine and C-RP). eGFR was calculated by means of three formulas, namely the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) [19], Cockcroft–Gault [20] and Modification of Diet in Renal Disease (MDRD) [21] formulas. The formula having the best performance in estimating dalbavancin clearance (CL) was chosen. eGFR was normalized to 1.73 m^2, in agreement with what we have just done in our previous dalbavancin population PK model [5], or used without body surface area indexation.

The overall number of administered dalbavancin doses was established by the treating physician based on a test of cure (TOC), as previously described [22]. Briefly, TOC was assessed monthly by means of an ambulatory visit and was defined as positive whenever local (rubor, tumor, calor, dolor) and systemic (fever and pain) signs of infection disappeared, CRP values became normal, and there were no suggestive findings of infection on imaging studies. The dalbavancin treatment period was defined as the elapsed time between starting dalbavancin treatment and the date of positive TOC [22].

2.2 Population Pharmacokinetic and Pharmacodynamic Modeling

A PK/PD model was adopted to simultaneously fit both PK and PD data. Model structure is shown in electronic supplementary material (ESM) Fig. S1. The non-linear mixed-effects modeling using the stochastic approximation maximization (SAEM) algorithm implemented within the Monolix software (version 2023R1; Lixofit, Antony, France) was used for the analysis.

The structural PK model was based on a previous population PK model from our group including 69 patients having different types of subacute or chronic infections and 289 drug concentrations [5]. That study showed that the best model describing dalbavancin concentrations was the two-compartment linear model with first-order rate transfer constants between the central and peripheral compartments, and first-order rate constant of elimination from the central compartment [5]. The PK estimates of that model were used as initial values for the current model, and all the population PK parameters were re-estimated. An initial PK/PD model without covariates was built and fitted to the data. The following clinical covariates were then tested on the PK parameters: sex, weight, height, serum creatinine, and eGFR. C-RP was also tested as a continuous covariate on dalbavancin CL. Finally, a full PK/PD model that included the significantly retained covariates was built and used as the final model. The relationship between covariates and PK parameters was tested according to an exponential relationship.

PD modeling was performed using an indirect turnover model with full inhibition of C-RP production as follows (Eq. 1):

$$\frac{dR}{dt} = kin \times \left(1 - \frac{Cp}{IC50 + Cp}\right) - kout \times R, \quad (1)$$

where R represents the response (i.e., C-RP concentration in plasma); $\frac{dR}{dt}$ represents the changing rate of C-RP concentration in plasma relative to time; Cp is the dalbavancin total plasma concentration; kin and $kout$ represent the increasing and decreasing elimination rates of C-RP concentration in plasma, respectively; and IC_{50} is the dalbavancin concentration causing the half-maximal rate of C-RP decline. C-RP values at time zero ($R0$), i.e. when starting dalbavancin treatment, were considered as the baseline values for modeling As C-RP concentration

at baseline is independent from dalbavancin concentration, R0 was fixed to the value of C-RP for the *i*th individual at time zero, therefore only the inhibition production of C-RP is estimated. *R0* is equivalent to the *kin/kout* ratio ($R0 = kin/kout$). The choice of this type of model was based on the biological plausibility and on previous population PK/PD studies that investigated the relationship between vancomycin or teicoplanin concentrations and C-RP [23, 24].

All individual parameters were considered to be log-normally distributed, random effects were normally distributed, and an exponential model was used for describing the individual parameter estimates. Different error models (constant, proportional, or combined error model) were tested for describing the residual variability.

Covariate analysis was conducted according to a forward/backward process. In the forward step, the correlation between each covariate and the random effect of the estimated PK parameter was tested. In particular, Pearson's correlation test was used to test the null hypothesis that the correlation coefficient between the random effects (calculated from the individual parameters sampled from the conditional distribution) and the covariate values is zero. In the backward step, each covariate is tested for removal from the full covariate model based on the Wald test. Both tests were considered positive when the *p*-value was < 0.05. Finally, a covariate was included in the final model if a decrease of ≥ 3.84 points in the objective function value (OFV), coupled with a reduction in the Akaike information criteria (AIC) and Bayesian information criteria (BIC), were observed with respect to the base model. Of note, these two latter criteria are indicated in the case of models including covariates for adjusting for model complexity.

Reliability of the PK/PD model was based on the observation of < 30–40% relative standard errors (RSE%) of the PK and PD estimates, and on the adequacy of the following goodness-of-fit plots: observation versus population and individual predictions, usual residual-based plots (individual- and population-weighted residuals), and prediction-corrected visual predictive check (pcVPC).

Overall, 1000 non-parametric bootstrap iterations with resampling for each estimated PK and PD parameter were simulated using the Rsmlx package of R (R speaks Monolix), and the median (interquartile range) were reported. The observed versus predicted concentration for both the PK/PD and the pcVPC were replotted in R.

2.3 Monte Carlo Simulation

First, the relationship between dalbavancin concentrations and the extent of C-RP production inhibition was assessed by means of 10,000 subject Monte Carlo simulations based on the population variability and between-subject variability resulting from the PD model. The median (5th–95th percentiles) probability of inhibiting CRP production was calculated in the presence of dalbavancin concentrations ranging from 0.5 to 100 mg/L, with 0.5 mg/L being the lowest quantifiable dalbavancin concentration.

Second, for each of the tested dosing regimens, the median of the percentage reduction extent of the C-RP value at each specific date versus baseline was assessed. The probability of achieving definitive C-RP production inhibition (defined as values < 1 mg/dL) was also assessed.

Three different dosing regimens of a cumulative dalbavancin dose of 3000 mg over 3 weeks, according to what was proposed by Senneville et al. [16] (namely 1500 mg on day 1 + 1500 mg on day 8; 1500 mg on day 1 + 1500 mg on day 15; 1500 mg on day 1 + 500 mg on day 8 + 500 mg on day 15 + 500 mg on day 22) were tested in relation to four different classes of renal function (eGFR of 0–29, 30–59, 60–89, and 90–120 mL/min). An additional dose of 1500 mg administered on day 43 was simulated to test the same objectives in the case of patients clinically needing an extension of treatment duration over 6 weeks.

Monte Carlo simulations based on the final PK/PD model were performed by means of Simulix 2023R1. A total of 10,000 C-RP concentration versus time profiles were generated for each dalbavancin dosing regimen in relation to the different classes of eGFR. The estimated PK/PD population parameter values with interindividual variability (omega values) were considered for simulations. The same seed of reproducibility was used for all simulations.

3 Results

3.1 Population Characteristics

A total of 45 patients (31 males, 68.9%) were included in this analysis. Patient demographic and clinical characteristics are summarized in Table 1. Median (minimum–maximum range) age, weight and eGFR were 61 (18–80) years, 78 (50–110) kg and 93.0 (33.0–144.0) mL/min/1.73 m^2, respectively.

Approximately half of the patients (23/45, 51.1%) had prosthetic joint infections (11 prosthetic hip infections, 8 prosthetic knee infections, 4 implant-related infections). Overall, spondylodiscitis, osteomyelitis, and pseudoarthrosis accounted for another 40% of cases (18/45), and septic arthritis accounted for the remaining 8.9% of cases (4/45). Microbiological isolates were identified in 40 cases (40/45, 88.9%; 35 monomicrobial and 5 polymicrobial). Specifically, there were 19 methicillin-resistant coagulase-negative staphylococci (MR-CoNS), 10 MRSA, 10

Table 1 Demographics and clinical characteristics of the population

Characteristic	Value
Total number of patients	45
Age, years	61 (18–80)
Sex, M/F	31/14 (68.9/31.1)
Weight, kg	78 (50–110)
BMI, kg/m^2	27.4 (18.8–42.9)
eGFR, mL/min/1.73 m^2	93 (33–144)
Type of infection	
Prosthetic joint infection	23 (51.1)
Spondylodiscitis	8 (17.8)
Infected pseudoarthrosis non-unions	6 (13.3)
Osteomyelitis	4 (8.9)
Septic arthritis	4 (8.9)
Dalbavancin treatment	
Total dose, mg	3000 (3000–7500)
No. of TDM assessments per patient	4 (1–8)
Pharmacodynamics	
C-RP baseline value, mg/dL	2.67 (1.1–30.6)
No. of subsequent C-RP assessments per patient	4 (1–8)
Clinical outcome	
Cured	41 (91.1)
Failed	4 (8.9)

Data are expressed as median (minimum–maximum) for continuous variables and number (%) for dichotomous variables

BMI body mass index, *C-RP* C-reactive protein, *eGFR* estimated glomerular filtration rate, *F* female, *M* male, *TDM* therapeutic drug monitoring

methicillin-susceptible (MS)-CoNS and 6 MS-*Staphylococcus aureus*.

The median (minimum-maximum), per treatment course, total dalbavancin dose was 3000 (3000–7500) mg. Most patients (25/45, 55.6%) received only two 1500 mg doses 1-week apart, whereas 16/45 (35.6%) patients received three 1500 mg doses and four ≥ 4 1500 mg doses (4/45, 8.9%). TOC was positive in 41/45 (91.1%) patients. Among the four patients who did not respond to treatment, despite a partial reduction in C-RP, TOC was negative, therefore three patients had to switch to another antimicrobial treatment and one did not have final resolution of signs and symptoms.

3.2 Population Pharmacokinetic and Pharmacodynamic Modeling

A total of 175 dalbavancin and 211 C-RP plasma concentrations were included in the PK/PD model. The only covariate significantly associated with dalbavancin CL in the base two-compartment model was eGFR, estimated by means of the CKD-EPI formula. After implementing eGFR as a covariate on dalbavancin CL, a decrease of 23.18, 21.17, and 19.71 points were observed in the OFV, AIC and BIC, respectively. The relationship between individual CL and eGFR was expressed using the following formula: $CL = 0.030 \times e^{0.0042 \times eGFR}$.

The final population PK/PD model well described the observed dalbavancin concentrations (R^2 of observed versus population-predicted concentrations, and observed versus individual-predicted concentrations of 0.85 and 0.94, respectively) [ESM Figs. S2A and S2B]. The population parameter estimates are summarized in Table 2. It is worth noting that the non-renal CL of dalbavancin was 0.031 L/h, while the total CL (non-renal and renal) obtained from the individual posterior estimates was 0.045 L/h. The PK/PD model fit to the C-RP data was poor for the observed versus population-predicted concentrations ($R^2 = 0.22$) [ESM Figs. S2C and S3] but high for the observed versus individual-predicted concentrations ($R^2 = 0.94$) [ESM Figs. S2D and S3]. No trend was observed in the individual weighted residuals (IWRES) versus both time and individual predictions, either for the PK or PD models (ESM Figs. S4 and S5, respectively). Individual PK and PD fittings are reported in ESM Figs. S6 and S7, respectively. All the main parameter estimates had acceptable precision, being the RSE% of 30–40% and the bootstrap median values very close to the population estimates. The pcVPCs showed acceptable predictive performances of both dalbavancin concentrations (Fig. 1a) and C-RP concentrations (Fig. 1b), being the 10th, 50th and 90th percentiles of the observed data inside the simulated prediction intervals.

3.3 Monte Carlo Simulation

The relationship between total dalbavancin concentration and the extent of C-RP production inhibition is shown in Fig. 2. According to the model, the median (5–95 percentile) dalbavancin IC_{50}, namely the dalbavancin plasma concentration granting half-maximal C-RP production inhibition, was 0.70 (< 0.5–14.5) mg/L.

Figure 3 shows the percentage reduction from baseline of the median C-RP profile in relation to three different schedules of a total dose of 3000 mg over the first 3 weeks of treatment. Interestingly, with all of the tested dosing regimens, the percentage reduction from baseline of the median C-RP at day 42 was ≥ 90%. Figure 4 shows that in cases having a clinical need for prolonging effective treatment over 6 weeks, an additional 1500 mg dalbavancin dose administered at day 43 may extend target duration up to day 63.

The probability of achieving a C-RP concentration < 1 mg/L that was associated with the tested regimens in relation to the different eGFR classes is reported in Tables 3 and 4. The three dosing schedules of 3000 mg over 3 weeks

Table 2 Summary of the population pharmacokinetic and pharmacodynamic model

Parameter	PK/PD model		Bootstrap results	
	Value	%RSE	Median	5th–95th percentiles
Fixed-effects				
CL (L/h)	0.031	15.4	0.028	0.02–0.03
β_eGFR	0.0042	32.8	0.005	0.003–0.007
V_1 (L)	5.93	4.8	5.98	5.43–6.32
Q (L/h)	0.038	34.9	0.04	0.02–0.19
V_2 (L)	9.55	14.2	9.08	6.81–25.59
k_{out} (h^{-1})	0.0037	11.6	0.0038	0.003–0.005
IC_{50} (mg/L)	0.70	35.0	0.58	0.35–1.16
SD of the random effects				
ω CL	0.12	334	0.11	0.05–0.18
ω V_1	0.14	42.7	0.13	0.09–0.27
ω Q	0.70	39.9	0.57	0.29–1.33
ω V_2	0.47	32.5	0.60	0.39–1.40
ω k_{out}	0.63	13.4	0.62	0.46–0.83
ω IC_{50}	1.5	17.9	1.38	1.09–1.83
Residual variability				
b_1	0.27	8.9	0.25	0.17–0.29
b_2	0.32	6.3	0.32	0.24–0.35

b_1 and b_2 proportional residual errors of the PK and PD models, respectively, *β_eGFR* coefficient of eGFR when dalbavancin CL was scaled to eGFR ($CL = 0.030 \times e^{0.0042 \times eGFR}$), *CL* non-renal clearance of dalbavancin, *C-RP* C-reactive protein, *eGFR* estimated glomerular filtration rate, IC_{50} dalbavancin concentration causing the half-maximal rate of C-RP decline, *PD* pharmacodynamic, *PK* pharmacokinetic, *RSE* relative standard error, *SD* standard deviation, V_1 and V_2 are the volume of distribution of the central and peripheral compartments, respectively.

Only k_{out} is estimated. k_{in} derives from a parameter transformation ($k_{in} = R0 \times k_{out}$). R0 was fixed to the C-RP value at time zero of each individual

of treatment were associated with a probability of between 74.5% and 81.7% in attaining C-RP levels < 1 mg/dL at day 42 in the various eGFR classes. An additional dalbavancin 1500 mg dose at day 43 was associated with an increase in the probability of attaining C-RP levels < 1 mg/dL at day 63 ranging between 84.9% and 89.9% in the different eGFR classes.

4 Discussion

To the best of our knowledge, this is the first study to develop a population PK/PD model focused on assessing the relationship between dalbavancin exposure and C-RP production inhibition over time in real-life patients treated with dalbavancin for staphylococcal osteoarticular infections.

The PK of dalbavancin was described by a two-compartment model, and the population estimates of CL (0.045 L/h vs. 0.043–0.057 L/h) and V (18 L vs. 15–15.9 L) were consistent with those observed in previous studies [5, 25, 26].

The PD of dalbavancin exposure versus C-RP production inhibition was adequately described by an indirect turnover I_{max} model with full inhibition of the C-RP production. This PD model was adopted for describing the relationship between vancomycin or teicoplanin and C-RP in previous investigations [23, 24], and its application for dalbavancin seems plausible. The model estimated that the median total dalbavancin IC_{50} on C-RP production was as low as 0.70 mg/L, but with quite a wide 5–95% confidence interval (CI). Considering plasma protein binding of 93% [15], this value may correspond to a free IC_{50} of 0.05 mg/L, which is in agreement with the MIC values usually exhibited by dalbavancin against staphylococci. A recent survey investigating dalbavancin susceptibility against a large collection of Gram-positives ($n = 8643$) yielded from patients with bloodstream infections admitted to 72 US and European medical centers showed that the MIC_{90} of dalbavancin was 0.03 mg/L against MRSA and methicillin-sensitive *Staphylococcus aureus* (MSSA), and 0.06 mg/L against *Staphylococcus epidermidis* [27].

Nevertheless, the 5–95% CI of the population total dalbavancin IC_{50} on C-RP production estimated by our model was quite wide. This may suggest that the response to dalbavancin treatment may greatly vary among patients with osteoarticular infections, depending on both the type of osteoarticular infection and the history of the disease. Whereas median patients' total dalbavancin concentrations as low as 0.5–1 mg/L may be sufficient for effectively suppressing the inflammatory response over time, in those with the most challenging clinical scenarios, the drug concentration should be much higher, as identified by the 95% CI. This is in line with our previous findings concerning long-term treatment of subacute/chronic infections with dalbavancin [5]. The PD target of dalbavancin efficacy against staphylococcal infections is an $fAUC_{24}$/MIC ratio > 111.1 [14]. We previously showed that from a clinical standpoint, total dalbavancin concentrations ≥ 8.04 mg/L may grant maintenance of this PD target over time when dealing with infections caused by less susceptible staphylococcal strains having an MIC value near to the EUCAST clinical breakpoint of dalbavancin for staphylococci, namely 0.125 mg/L [15]. Conversely, it should be expected that whenever dealing with very susceptible strains having MIC values ≤0.015 mg/L, the total dalbavancin concentrations needed for achieving this goal could be much lower, namely around 0.5–1 mg/L. A high interindividual variability was also observed in the C-RP

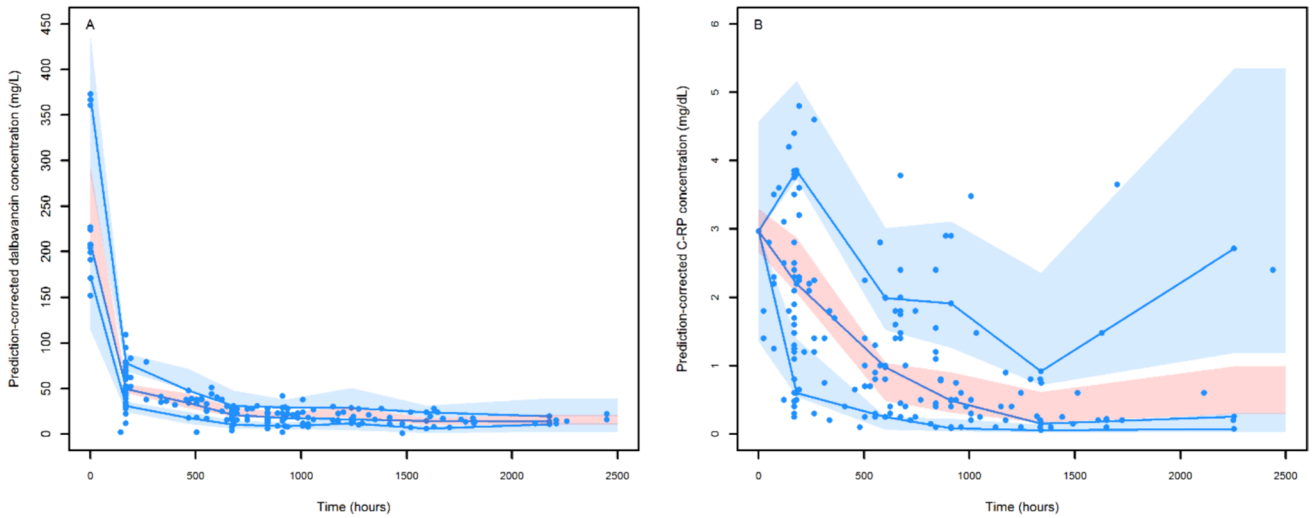

Fig. 1 Prediction-corrected visual predictive check for the population (**a**) pharmacokinetic and (**b**) pharmacodynamic models. By default, three prediction intervals are displayed, one for each of the following percentiles of observed data: 10th, 50th and 90th percentiles. Prediction intervals are estimated across all simulated data and are displayed as colored areas (pink for the 50th percentile, blue for the 10th and 90th percentiles). Each prediction interval is computed with a level of 90%. The continuous blue lines indicate the 10th, 50th and 90th percentiles for observed data. *C-RP* C-reactive protein

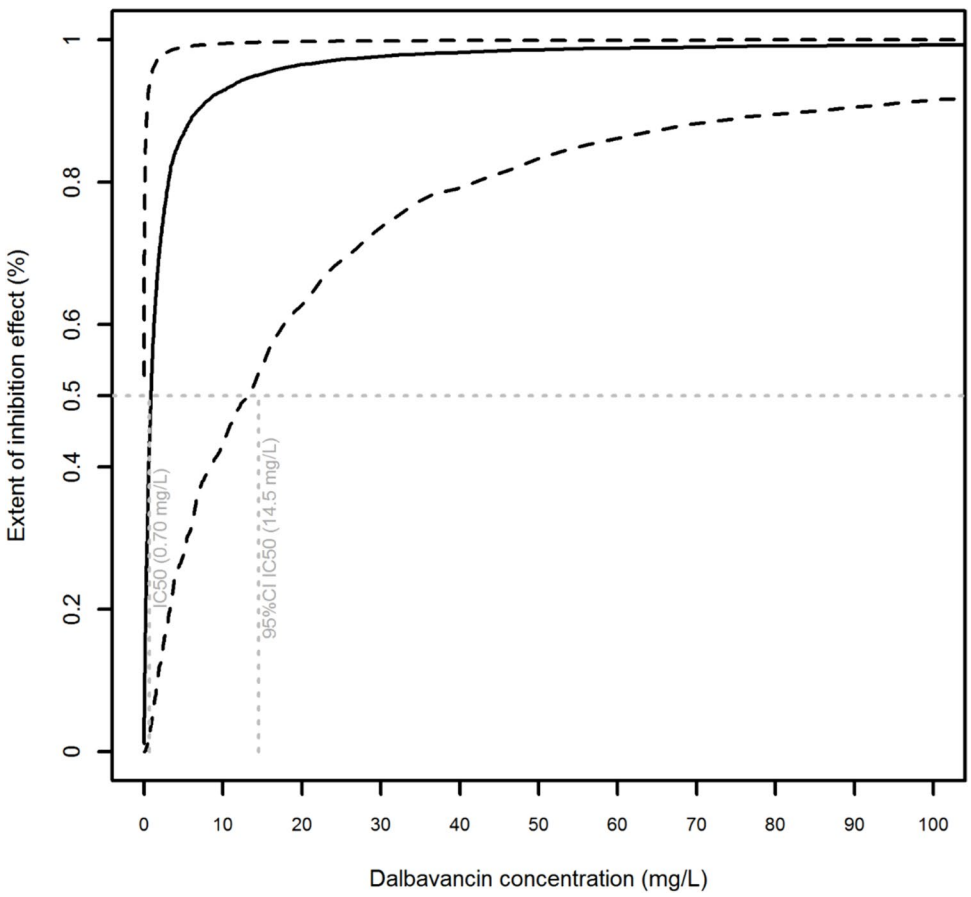

Fig. 2 Relationship between dalbavancin concentration and extent of inhibition effect for C-RP production after 10,000 Monte Carlo simulations using the population values and between-subject variability from the PK/PD model. The solid and dashed lines represent the median and 90% prediction interval of the extent of the inhibition effect, respectively. The gray vertical dotted lines represent the IC_{50} (0.70 mg/L) and the 95% percentile of the IC_{50} (14.5 mg/L). *C-RP* C-reactive protein, *IC_{50}* half maximal inhibitory concentration, *PD* pharmacodynamic, *PK* pharmacokinetic

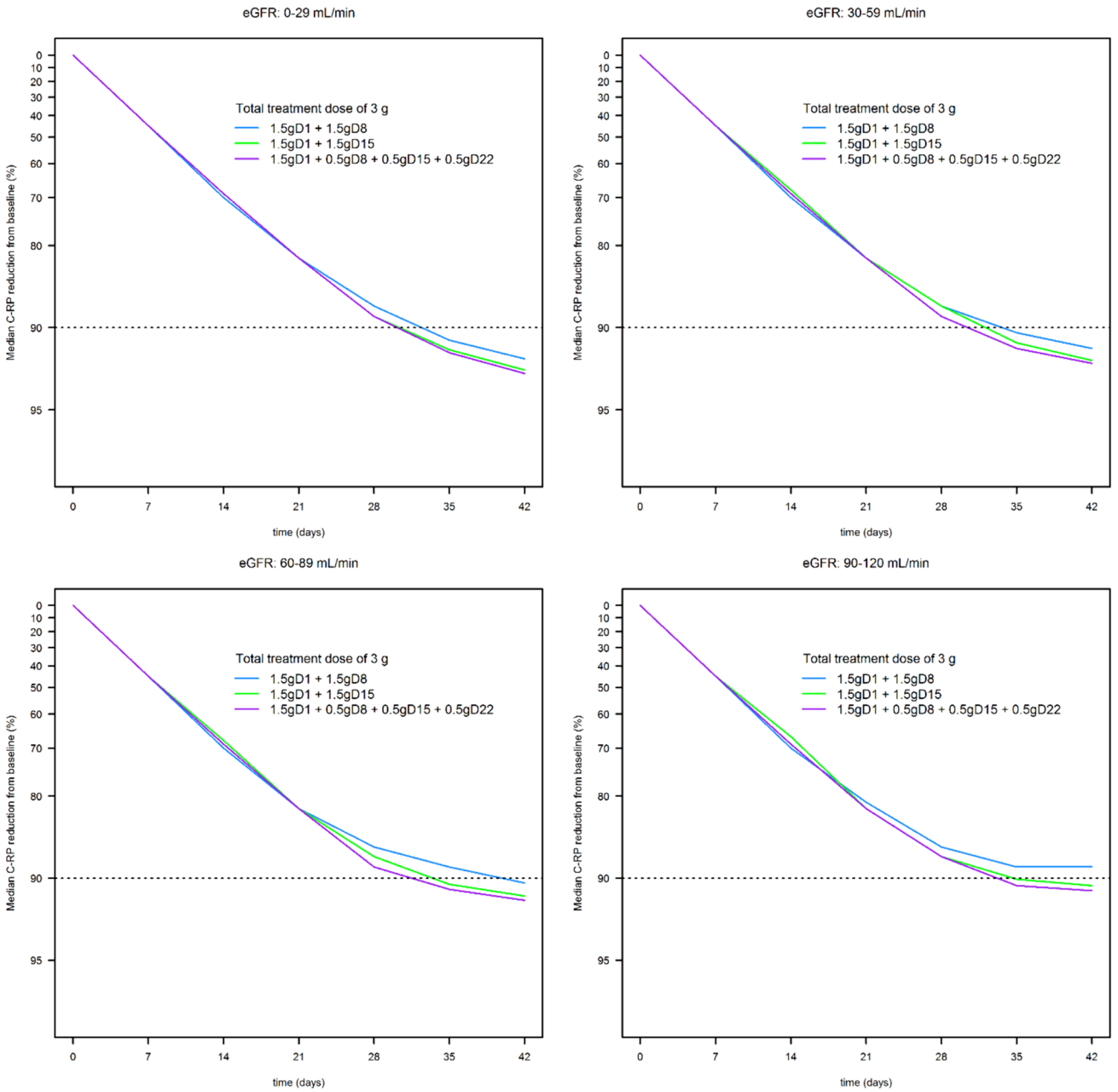

Fig. 3 Percentage reduction of estimated median C-RP over time after administering a total dalbavancin dose of 3000 mg in the first 3 weeks in relation to different schedule regimens and classes of renal function. Horizonal dotted lines identify a 90% probability of C-RP reduction. In the eGFR 60–89 mL/min/1.73 m^2 class, the 1.5 g D1 + 1.5 g D8 group is overlaid to that of the 1.5 g D1 + 0.5 g D8 + 0.5 g D15 + 0.5 g D22 group. *C-RP* C-reactive protein, *D* day, *eGFR* estimated glomerular filtration rate

baseline estimate (R0), but this is related to each patient's clinical condition before starting dalbavancin treatment.

Our findings may help clinicians in assessing patient's response to treatment, as C-RP is a major inflammatory biomarker produced in response to infection [28–30]. First, when administering a total dalbavancin dose of 3000 mg over 3 weeks, the time needed for obtaining a > 90% C-RP decrease versus baseline may be approximately 5–6 weeks. Importantly, this target attainment may be obtained in a similar fashion, with all three of the tested scheduled dosing regimens (namely 1500 mg on day 1 + 1500 mg on day 8, 1500 mg on day 1 + 1500 mg on day 15, and 1500 mg on day 1 + 500 mg on days 8, 15 and 22). This may be explained by the fact that all of these regimens are always expected to maintain total dalbavancin concentrations above the 95% CI of IC_{50} on C-RP production. This may allow

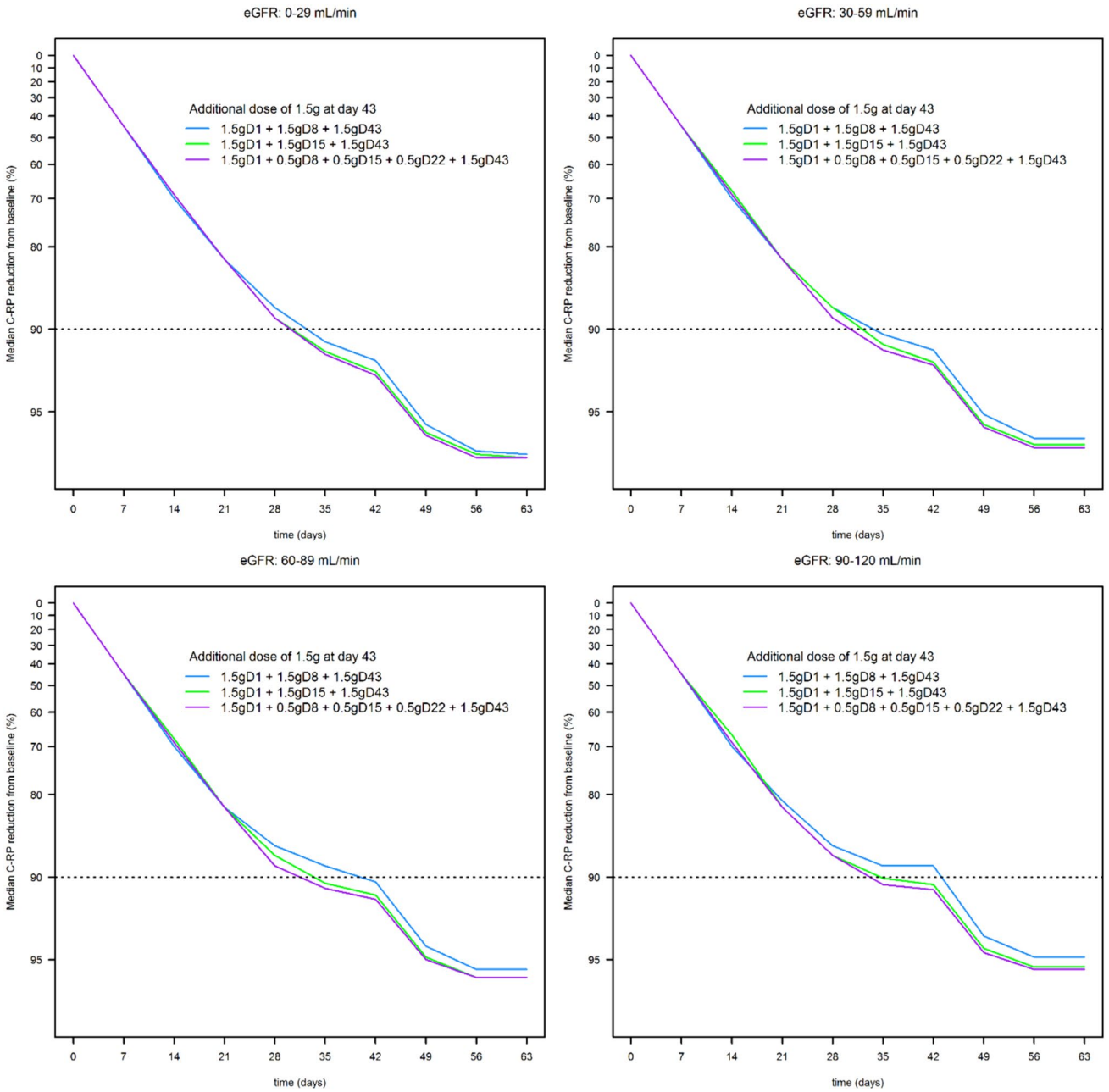

Fig. 4 Percentage reduction of estimated median C-RP over time after an initial total dalbavancin dose of 3000 mg in the first 3 weeks in relation to different schedule regimens followed by an additional 1500 mg dose at D43 in relation to different classes of renal function. Horizonal dotted lines identify a 90% probability of C-RP reduction. *C-RP* C-reactive protein, *D* day, *eGFR* estimated glomerular filtration rate

clinicians to choose the preferred dosing schedule regimen based mainly on the specific patient handling tasks and needs more so than on efficacy issues. Second, in patients clinically needing longer treatments, an additional 1500 mg dose at day 43 may prolong C-RP production inhibition for another 3 weeks.

TDM may represent a helpful tool in assessing the adequacy of dalbavancin exposure by targeting the PK/PD target of efficacy against staphylococci, either empirically (focusing on the EUCAST clinical breakpoint) or precisely (whenever the punctual MIC value of the clinical isolate was available).

Dalbavancin off-label use in osteoarticular infections is ever growing, and although the management of osteoarticular infections may differ among centers, the therapeutic approach to dalbavancin is quite shared. In fact, in a recent

Table 3 Probability of attaining definitive C-RP concentrations < 1 mg/dL at subsequent timepoints with different tested dalbavancin dosing regimens for treating osteoarticular infections in patients with severe and moderate renal dysfunction

Days	Dalbavancin dosing regimens in patients with eGFR < 30 mL/min			Dalbavancin dosing regimens in patients with eGFR 30–59 mL/min		
	1500 mg d1 + 1500 mg d8	1500 mg d1 + 1500 mg d15	1500 mg d1 + 500 mg d8 + 500 mg d15 + 500 mg d22	1500 mg d1 + 1500 mg d8	1500 mg d1 + 1500 mg d15	1500 mg d1 + 500 mg d8 + 500 mg d15 + 500 mg d22
0	0.0	0.0	0.0	0.0	0.0	0.0
7	28.4	28.4	28.4	28.4	28.4	28.4
14	50.6	48.7	49.9	50.6	48.2	49.7
21	64.6	64.7	64.5	64.5	64.6	64.4
28	72.6	73.6	74.1	72.3	73.2	73.7
35	77.5	78.6	79.2	76.5	77.9	78.4
42	79.9	81.2	81.7	78.5	79.8	80.4
+1500 mg d43						
49	86.7	87.4	87.6	85.2	86.1	86.4
56	88.9	89.4	89.6	87.4	88.0	88.2
63	89.3	89.7	89.9	87.7	88.2	88.4

Dosing regimens are expressed as dalbavancin dose (mg) at day *x*. An additional dose of 1500 mg on d43 was also included

C-RP C-reactive protein, *d* day, *eGFR* estimated glomerular filtration rate

Table 4 Probability of attaining definitive C-RP concentrations < 1 mg/dL at subsequent timepoints with different tested dalbavancin dosing regimens for treating osteoarticular infections in patients with mild renal dysfunction and normal renal function

Days	Dalbavancin dosing regimens in patients with eGFR 60–89 mL/min			Dalbavancin dosing regimens in patients with eGFR 90-120 mL/min		
	1500 mg d1 + 1500 mg d8	1500 mg d1 + 1500 mg d15	1500 mg d1 + 500 mg d8 + 500 mg d15 + 500 mg d22	1500 mg d1 + 1500 mg d8	1500 mg d1 + 1500 mg d15	1500 mg d1 + 500 mg d8 + 500 mg d15 + 500 mg d22
0	0.0	0.0	0.0	0.0	0.0	0.0
7	28.2	28.2	28.2	28.2	28.2	28.2
14	50.5	48.2	49.7	50.5	47.9	49.7
21	63.2	63.4	63.2	63.1	63.3	63.2
28	70.8	72.1	72.8	70.2	71.6	72.5
35	74.6	76.2	77.1	73.8	75.8	76.7
42	75.8	77.7	78.4	74.5	76.7	77.4
+1500 mg d43						
49	83.6	84.8	85.3	83.1	84.5	84.9
56	86.3	86.9	87.3	85.4	86.2	86.4
63	86.2	86.9	86.9	84.9	85.5	85.7

Dosing regimens are expressed as dalbavancin dose (mg) at day *x*. An additional dose of 1500 mg at d43 was also included

C-RP C-reactive protein, *d* day, *eGFR* estimated glomerular filtration rate

review on dalbavancin use in osteoarticular infections that included 23 clinical studies and 450 patients, it was shown that dalbavancin use was preceded by surgical interventions for proper source control in 69.2% of cases, and by a previous in-hospital antimicrobial treatment in 65.3% of subjects [31]. These data may support the utility of this model in a wide range of clinical scenarios. However, it should be kept in mind that C-RP production may sometimes be inhibited only partially, or may even not be suppressed, as different factors may affect clinical outcome in patients with osteoarticular infections. For instance, a retrospective cohort study conducted among 19 European hospitals that included 120 patients with *S. aureus* prosthetic joint infections showed that the co-presence of bacteremia, the need for additional

debridement, and the time from symptom onset to surgery may be associated with failure in suppressing C-RP production [32].

We are aware that this study presents some limitations. The retrospective study design and the heterogeneity of the patient case mix should be acknowledged, although similar pre-dalbavancin treatment approaches were adopted for all patients (surgery followed by a daptomycin-based combination regimen). Moreover, the absence of specific MIC values of the clinical isolates by means of the broth microdilution method precluded us from more adequately investigating the relationship between the PK/PD target of efficacy and C-RP production inhibition, even if a punctual MIC may still be imprecise [33]. The fact that our model was based on a moderately wide range of baseline C-RP values could limit the generalizability of the findings to patients having very high baseline C-RP values. Lastly, we recognize that our model was based on sparse sampling from real-world data. If this approach might, on the one hand, better capture interindividual variability it may, on the other hand, reduce robustness of the estimates.

5 Conclusion

Our study developed a PK/PD model of dalbavancin and C-RP in patients with staphylococcal osteoarticular infections. Our findings showed that targeting total dalbavancin plasma concentrations at > 14.5 mg/L throughout treatment may grant C-RP production inhibition over time in the vast majority of cases. This is important information because it allowed us to identify a threshold of efficacy based on real-word clinical patients that may be adopted to individualize dalbavancin treatment. This approach may be considered reliable for patients with staphylococcal osteoarticular infections caused by dalbavancin susceptible strains and a baseline C-RP concentration < 30.6 mg/dL. Moreover, we also showed that a total dalbavancin dose of 3000 mg administered in the first 3 weeks may lead to a more than 90% C-RP decrease versus baseline in approximately 5–6 weeks, depending on patient renal function. In patients needing treatment prolongation, an additional 1500 mg dose after this period may allow C-RP production inhibition to be extended for other 3 weeks. This is also an important piece of information for assessing patient response to treatment that is still based on monitoring C-RP over time. Prospective studies are warranted to confirm the reliability of our findings.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40262-024-01410-2.

Declarations

Funding Open access funding provided by Alma Mater Studiorum - Università di Bologna within the CRUI-CARE Agreement.

Author Contributions PGC, FP, and PV conceptualized the work. PGC, ST, EZ, and FP wrote the manuscript. PGC, ST, and EZ collected the clinical data and performed the analysis. FP and PV supervised the entire work. All authors have read and agreed to the published version of this manuscript.

Conflicts of Interest Pier Giorgio Cojutti received fees from Angelini, Shionogi, Pfizer, and MSD outside of the submitted work. Federico Pea reports personal fees from Angelini, Basilea Pharmaceutica, Gilead, Hikma, MSD, Pfizer, Sanofi-Aventis, Shionogi, Thermo Fisher, and Accelerate Diagnostics, outside the submitted work; has participated in speakers' bureaus for Accelerate Diagnostics, Angelini, Basilea Pharmaceutica, Gilead, Hikma, MSD, Pfizer, Sanofi-Aventis, Shionogi, and Thermo Fisher; and has been a consultant for Angelini, Basilea Pharmaceutica, Gilead, MSD, Pfizer, and Shionogi, outside the submitted work. Pierluigi Viale has served as a consultant for bioMérieux, Gilead, Merck Sharp and Dohme, Nabriva, Nordic Pharma, Pfizer, Thermo-Fisher, and Venatorx, and has received payment for serving on the speakers' bureaus for Correvio, Gilead, Merck Sharp, and Dohme, Nordic Pharma, and Pfizer, outside the submitted work. Sara Tedeschi and Eleonora Zamparini report no potential conflicts of interest that may be relevant to the contents of this study.

Institutional Review Board Statement This study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of the IRCCS, Azienda Ospedaliero-Universitaria di Bologna (protocol code 897/2021/Oss/AOUBo).

Informed Consent Statement Patient consent was waived due to the retrospective and observational nature of the present investigation, according to hospital agreements.

Data Availability Statement The data presented in this study are available upon request from the corresponding author. The data are not publicly available due to privacy concerns. The de-identified individual participant data that underlie the results reported in this article (including text, tables, and figures) will be made available, together with the research protocol for non-commercial, academic purposes. Additional supporting documents may be available on request.

Consent for Publication Not applicable.

Code Availability Not applicable.

References

1. Smith JR, Roberts KD, Rybak MJ. Dalbavancin: A novel lipoglycopeptide antibiotic with extended activity against gram-positive infections. Infect Dis Ther. 2015;4(3):245–58.
2. Molina KC, Miller MA, Mueller SW, Van Matre ET, Krsak M, Kiser TH. Clinical pharmacokinetics and pharmacodynamics of dalbavancin. Clin Pharmacokinet. 2022;61(3):363–74.
3. Oliva A, Stefani S, Venditti M, Di Domenico EG. Biofilm-related infections in gram-positive bacteria and the potential role of the long-acting agent dalbavancin. Front Microbiol. 2021;12: 749685.
4. Dunne MW, Puttagunta S, Sprenger CR, Rubino C, Van Wart S, Baldassarre J. Extended-duration dosing and distribution of dalbavancin into bone and articular tissue. Antimicrob Agents Chemother. 2015;59(4):1849–55.
5. Cojutti PG, Tedeschi S, Gatti M, Zamparini E, Meschiari M, Siega PD, et al. Population pharmacokinetic and pharmacodynamic analysis of dalbavancin for long-term treatment of subacute and/or chronic infectious diseases: the major role of therapeutic drug monitoring. Antibiotics. 2022;11(8):996.
6. Morata L, Cobo J, Fernández-Sampedro M, Guisado Vasco P, Ruano E, Lora-Tamayo J, et al. Safety and efficacy of prolonged use of dalbavancin in bone and joint infections. Antimicrob Agents Chemother. 2019;63(5):e02280-18.
7. Almangour TA, Perry GK, Terriff CM, Alhifany AA, Kaye KS. Dalbavancin for the management of gram-positive osteomyelitis: Effectiveness and potential utility. Diagn Microbiol Infect Dis. 2019;93(3):213–8.
8. Berbari EF, Kanj SS, Kowalski TJ, Darouiche RO, Widmer AF, Schmitt SK, et al. 2015 Infectious Diseases Society of America (IDSA) Clinical Practice Guidelines for the Diagnosis and Treatment of Native Vertebral Osteomyelitis in Adults. Clin Infect Dis. 2015;61(6):e26-46.
9. Bernard L, Arvieux C, Brunschweiler B, Touchais S, Ansart S, Bru JP, et al. Antibiotic therapy for 6 or 12 weeks for prosthetic joint infection. N Engl J Med. 2021;384(21):1991–2001.
10. Zimmerli W. Clinical practice. Vertebral osteomyelitis. N Engl J Med. 2010;362(11):1022–9.
11. Zimmerli W, Trampuz A, Ochsner PE. Prosthetic-joint infections. N Engl J Med. 2004;351(16):1645–54.
12. Dimopoulou D, Mantadakis E, Koutserimpas C, Samonis G. A narrative review on the role of dalbavancin in the treatment of bone and joint infections. Antibiotics (Basel). 2023;12(10):1492.
13. Zhanel GG, Calic D, Schweizer F, Zelenitsky S, Adam H, Lagacé-Wiens PR, et al. New lipoglycopeptides: a comparative review of dalbavancin, oritavancin and telavancin. Drugs. 2010;70(7):859–86.
14. Lepak A, Marchillo K, VanHecker J, Andes D. Impact of glycopeptide resistance in *Staphylococcus aureus* on the dalbavancin in vivo pharmacodynamic target. Antimicrob Agents Chemother. 2015;59(12):7833–6.
15. Cojutti PG, Rinaldi M, Gatti M, Tedeschi S, Viale P, Pea F. Usefulness of therapeutic drug monitoring in estimating the duration of dalbavancin optimal target attainment in staphylococcal osteoarticular infections: a proof-of-concept. Int J Antimicrob Agents. 2021;58(5): 106445.
16. Senneville E, Cuervo G, Gregoire M, Hidalgo-Tenorio C, Jehl F, Miro JM, et al. Expert opinion on dose regimen and therapeutic drug monitoring for long-term use of dalbavancin: expert review panel. Int J Antimicrob Agents. 2023;62(5): 106960.
17. Barone R, Conti M, Cojutti PG, Gatti M, Viale P, Pea F. Fast and simple liquid chromatography-isotope dilution tandem mass spectrometry method for therapeutic drug monitoring of dalbavancin in long-term treatment of subacute and/or chronic infections. Pharmaceutics. 2023;15(2):480.
18. Cojutti PG, Gatti M, Punt N, Douša J, Zamparini E, Tedeschi S, et al. Implementation and validation of a Bayesian method for accurately forecasting duration of optimal pharmacodynamic target attainment with dalbavancin during long-term use for subacute and chronic staphylococcal infections. Int J Antimicrob Agents. 2024;63(1): 107038.
19. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF, Feldman HI, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009;150(9):604–12.
20. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron. 1976;16(1):31–41.
21. Levey AS, Coresh J, Greene T, Stevens LA, Zhang YL, Hendriksen S, et al. Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. Ann Intern Med. 2006;145(4):247–54.
22. Gatti M, Viale P, Cojutti PG, Zamparini E, De Paolis M, Giannella M, et al. A descriptive case series of the relationship between maintenance of conservative PK/PD efficacy thresholds of dalbavancin over time and clinical outcome in long-term treatment of staphylococcal osteoarticular infections. Int J Antimicrob Agents. 2023;61(5): 106773.
23. Ogami C, Tsuji Y, Muraki Y, Mizoguchi A, Okuda M, To H. Population pharmacokinetics and pharmacodynamics of teicoplanin and C-reactive protein in hospitalized patients with gram-positive infections. Clin Pharmacol Drug Dev. 2020;9(2):175–88.
24. Rawson TM, Charani E, Moore LSP, Gilchrist M, Georgiou P, Hope W, et al. Exploring the use of C-reactive protein to estimate the pharmacodynamics of vancomycin. Ther Drug Monit. 2018;40(3):315–21.
25. Buckwalter M, Dowell JA. Population pharmacokinetic analysis of dalbavancin, a novel lipoglycopeptide. J Clin Pharmacol. 2005;45(11):1279–87.
26. Carrothers TJ, Chittenden JT, Critchley I. Dalbavancin population pharmacokinetic modeling and target attainment analysis. Clin Pharmacol Drug Dev. 2020;9(1):21–31.
27. Sader HS, Castanheira M, Huband MD, Shortridge D, Carvalhaes CG, Mendes RM. Antimicrobial activity of dalbavancin against Gram-positive bacteria isolated from patients hospitalized with bloodstream infection in United States and European medical centers (2018–2020). Eur J Clin Microbiol Infect Dis. 2022;41(5):867–73.
28. Piper KE, Fernandez-Sampedro M, Steckelberg KE, Mandrekar JN, Karau MJ, Steckelberg JM, et al. C-reactive protein, erythrocyte sedimentation rate and orthopedic implant infection. PLoS ONE. 2010;5(2): e9358.
29. Glehr M, Friesenbichler J, Hofmann G, Bernhardt GA, Zacherl M, Avian A, et al. Novel biomarkers to detect infection in revision hip and knee arthroplasties. Clin Orthop Relat Res. 2013;471(8):2621–8.
30. Wu Y, Zhou J, Liu R, Zeng Y, Sun K, Li M, et al. What Is the normal trajectory of C-reactive protein, erythrocyte sedimentation rate, plasma fibrinogen and D-Dimer after two-stage exchange for periprosthetic joint infection? Orthop Surg. 2022;14(11):2987–94.
31. Lovatti S, Tiecco G, Mulé A, Rossi L, Sforza A, Salvi M, et al. Dalbavancin in bone and joint infections: a systematic review. Pharmaceuticals (Basel). 2023;16(7):1005.
32. Espíndola R, Vella V, Benito N, Mur I, Tedeschi S, Zamparini E, et al. Rates and predictors of treatment failure in *Staphylococcus aureus* prosthetic joint infections according to different management strategies: a multinational cohort study-the ARTHR-IS Study Group. Infect Dis Ther. 2022;11(6):2177–203.
33. Kahlmeter G, Turnidge J. Wild-type distributions of minimum inhibitory concentrations and epidemiological cut-off values-laboratory and clinical utility. Clin Microbiol Rev. 2023;36(4): e0010022.