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Development of a dosing-adjustment tool for fluoroquinolones in osteoarticular infections: The Fluo-pop study

Florian Lemaitre [a,b,*], Fabien Fily [c,d], Jean-Baptiste Foulquier [a,b], Matthieu Revest [b,e,f], Vincent Jullien [g,h], Antoine Petitcollin [b], Pierre Tattevin [b,e,f], Camille Tron [a,b], Jean-Louis Polard [i], Marie-Clémence Verdier [a,b], Emmanuelle Comets [a,b], Denis Huten [i], Cédric Arvieux [e,f,j], Eric Bellissant [a,b], Bruno Laviolle [a,b]

[a] Univ Rennes, CHU Rennes, Inserm, EHESP, Irset (Institut de recherche en santé, environnement et travail) - UMR_S 1085, F-35000 Rennes, France
[b] INSERM, Centre d'Investigation Clinique, CIC 1414, F-35000 Rennes, France
[c] Epicentre, 55 rue Crozatier, 75012, Paris, France
[d] Infectious Diseases Unit, Broussais Hospital, Saint Malo, France
[e] Infectious Diseases and Intensive Care Unit, Pontchaillou University Hospital, Rennes, France
[f] University of Rennes, Inserm, BRM (Bacterial Regulatory RNAs and Medicine), UMR, France
[g] University Paris 13, groupe hospitalier Paris Seine-Saint-Denis, Assistance publique-Hôpitaux de Paris, 93000 Bobigny, France
[h] Molecular Mycology Unit-CNRS UMR 2000, Pasteur Institute, 75015 Paris, France
[i] Department of Orthopaedic Surgery and Traumatology, Pontchaillou University Hospital, 2 Avenue Henri Le Guilloux, 35203 Rennes, France
[j] Great West Reference centers for Complex Bone and Joint Infections (CRIOGO), France

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ABSTRACT

Fluoroquinolones efficacy depend on both the drug exposure and the level of drug resistance of the bacteria responsible for the infection. Specifically for the *Staphylococcus* species, which is the microorganism mainly involved in osteoarticular infections (OAI), in-vitro data reported that an AUC/MIC ratio above 115 h maximizes drug efficacy. However, data on OAI patients are lacking and a simple approach to access AUCs is still a clinical issue. We conducted a prospective, single-center study in 30 OAI patients hospitalized in the Rennes University Hospital to model ofloxacin pharmacokinetics and to define a limited sampling strategy (LSS) suitable for ofloxacin and levofloxacin treatments. Modeling was conducted with the Monolix software. The final model was externally validated using levofloxacin data. Monte-Carlo simulations were used to evaluate the probability of target attainment (PTA) of different dosing regimens. Two hundred and ninety-seven (297) ofloxacin concentrations were available for the pharmacokinetic modeling. Ofloxacin pharmacokinetics was best described using a bicompartmental model with a first order elimination, and a transit compartment model absorption. CKD-EPI and sex explained half of ofloxacin pharmacokinetic variability. For LSS, the 0, 1 h and 3 h sampling scheme resulted in the best approach both for BID and TID dosages (R^2 adjusted = 91.1% and 95.0%, outliers = 4.8% and 5.0%, respectively). PTA allows choosing the best drug and dosage according to various hypotheses. A simple 3-sample protocol (pre-dose, 1 h after intake and 3 h after intake) to estimate ofloxacin and levofloxacin AUC allows optimal drug dosage for the treatment of osteoarticular infections.

1. Introduction

Because bone is a tissue not easily accessible for drugs, few antibiotics are eligible for osteoarticular infections (OAI) treatment. Fluoroquinolones (FQ) pharmacokinetic profiles exhibit wide tissue diffusion resulting in high drug concentrations even in bone. These high concentrations at the infection sites lead to high efficacy even in complicated infections such as prosthetic joint infection [1]. Among FQs, ofloxacin, or its active enantiomer levofloxacin, exhibit good efficacy on commonly encountered microorganisms, particularly *Staphylococcus* species, and can be used depending on local drug availability or clinical team choice. Thus, FQ are recommended, together with rifampin, as the best option for the treatment of *Staphylococcus* sp. OAI [2,3]. Ofloxacin and levofloxacin efficacy depend on both the drug

* Correspondence to: Department of Pharmacology, Rennes University Hospital, 2, rue Henri Le Guilloux CEDEX, 35033 Rennes, France.
E-mail address: florian.lemaitre@chu-rennes.fr (F. Lemaitre).

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exposure and the level of drug resistance of the bacteria responsible for the infection. More precisely, the ratio of the area under the curve of the drug concentrations (AUC) over the minimal inhibitory concentration (MIC) of the causative bacteria is a predictor of treatment outcome. For example, an AUC/MIC above 125 h resulted in 80% success in treating infections (mainly pulmonary and urinary *Pseudomonas aeruginosa* infections) when using ciprofloxacin, another FQ [4]. Data with ofloxacin and levofloxacin are rather limited but showed in nosocomial pneumonia due to various pathogens that AUC/MIC ranging from 87 to 110 h were associated with favorable microbiological outcome [5]. More specifically to *Staphylococcus aureus,* in-vitro data suggested that an AUC/MIC ratio above 115 h allowed maximal drug efficacy [6]. Pharmacokinetic-pharmacodynamic (PK/PD) indexes are also related to resistance onset. For instance, the risk of resistance selection appears low when peak concentration (Cmax) over MIC ratio is above 10 and AUC/MIC is above 100 in gram-negative lower respiratory tract infections treated with ciprofloxacin [7].

Of note, there are limited reports available on PK/PD data related to OAI even though treatment failure in such infections can result in dramatic outcomes such as resistance, revision surgery, functional sequelae and patient's death. Thus, it is of the utmost importance to optimize drug exposure, particularly in these indications. However, individualized optimization requires determining AUC in patients treated with FQ. Due to the multiple blood samples needed to calculate AUC, a standard non compartmental approach is hardly feasible in clinical practice. One possible way to overcome this limitation is to develop a limited sampling strategy aiming to estimate AUC using a low number of blood samples, based on a model of the PK of ofloxacin and levofloxacin i.

The aim of the present study is therefore to model ofloxacin pharmacokinetics and to define a limited sampling strategy protocol in order to optimize and individualize ofloxacin and levofloxacin treatments in patients with OAI.

2. Methods

2.1. Study population and design

This prospective, single-center study included 30 patients hospitalized in Rennes University Hospital between June 2015 and December 2016. The inclusion criteria were an age over 18 years and a *Staphylococcus* sp.. OAI treated with oral ofloxacin in line with French recommendations [8,9], 200 mg twice daily (BID) or 200 mg three times daily (TID). All patients gave written informed consent. The FLUO-POP study (NCT02357407) was approved by the regulatory and ethics committee (ANSM 141294A-41 and CPP Ouest V 2014-004193-41) and was conducted in accordance with the declaration of Helsinki.

2.2. Determination of ofloxacin plasma concentration

Blood samples were collected on the fourth day after the first dose, immediately prior to dosing (0 h) and 0.5, 1, 1.5, 2, 2.5, 3, 5, 7, 8 and 12 h post-dose. Plasma ofloxacin concentrations were measured using a validated liquid chromatography tandem-mass spectrometry method according to international standards. Briefly, analysis was conducted on a chromatographic system composed of a Dionex U3000 liquid chromatography system (ThermoFisher Scientific, Waltham, USA) and an Endura mass spectrometer (ThermoFisher Scientific, Waltham, USA). The chromatographic separation was conducted on a hypersil gold C18 column (50 mm × 2.1 mm, particle size 3 μm, ThermoFisher Scientific, Waltham, USA) using two mobile phases of acid formic 0.1% in water (mobile phase A) and acetonitrile (mobile phase B). A flow of 500 μL/min of 95% of mobile phase A and 5% of mobile phase B was delivered by the chromatographic system and after injection of the 2 μL of samples, the flow was gradually modified to reach 66% of mobile phase A and 34% of mobile phase B after 2.5 min of run and then 25% of mobile phase A and 75% of mobile phase B at 2.6 min. Thereafter, the initial mobile phase gradient was slowly restored and reached at 3.7 min and maintained during 1.8 min for the system to re-equilibrate. The total chromatographic run was 5.5 min. This method has a concentration range going from 0.1 (limit of quantification) to 12 μg/mL for ofloxacin and levofloxacin. Within-day precision ranges from 4.3% to 5.2% (quality control levels at 0.25, 5 and 10 μg/mL). Within-day accuracy ranges from 5.5% to 8.3%. Between-day precision ranges from 4.6% to 6.5%. Between-day accuracy ranges from − 0.7–4.1%. Process efficiency was 106.4% at 0.25 μg/mL, 102.2% at 5.0 μg/mL and 105.0 at 10 μg/mL. There was a positive but constant matrix effect along the calibration range: 199.3% at 0.25 μg/mL, 199.9% at 5.0 μg/mL and 202.5% at 10.0 μg/mL.

2.3. Non compartmental analysis

Pharmacokinetic parameters were calculated using a non-compartmental approach with the ncappc R package [10].

2.4. Population pharmacokinetic analysis

The data was analysed using non-linear mixed effect models. The jth observed concentration at time t_{ij} in the ith patient ($i = 1,\ldots,N$, $j = 1,.n_i$), Y_{ij}, was modeled as a function of a structural model f, depending on individual parameters θ_i, covariates z_i, and a measurement error ε_{ij}:

$$Y_{ij} = f\left(t_{ij},\ \theta_i,\ z_i\right) + \varepsilon_{ij} \quad (1)$$

The interindividual variability of pharmacokinetic parameters was described using an exponential model:

$$\theta i = \theta_{TV} exp(\eta_i) \quad (2)$$

where θTV is the typical value of the parameter and η_i is the random effect for the ith patient. The values of η_i were assumed to be normally distributed, with mean 0 and variance ω2. We investigated the influence of covariates on parameters using exponential models: continuous covariates were centered over their median, multiplying (2) by a term $(COV_i / \text{med}(COV))^{\beta COV}$, and a reference category ($CAT_i = 0$) was chosen for categorical covariates, multiplying (2) by a parameter exp ($\beta_{CAT=1}$) for the other category.

For the residual error model, additive, proportional and mixed additive-proportional models were investigated.

For the structural model, one- and two-compartment models were investigated, with first-order elimination or nonlinear elimination process (Michaelis-Menten). Various absorption models were tested. Complex absorption models, including first-order absorption followed by zero-order absorption and zero-order absorption followed by first-order absorption, were also tested.

Parameters were estimated using the Stochastic Approximation Expectation Maximization (SAEM) algorithm implemented in the Monolix software (Monolix 2019R1) [11].

2.5. Model comparison and covariate selection

Structural, interindividual, interoccasion, residual error and covariate models were compared using the log-likelihood ratio test (LRT) for nested models and the Akaike information criterion (AIC) for non-nested models, defined as a function of the log-likelihood (LL) and the number of parameters in a model (p) as AIC = −2LL + 2p. An additional criterion for model selection was the precision of parameter estimates: variance parameters were fixed to 0 if their (relative standard error) RSE was larger than 30%.

The covariate model was investigated after the structural model had been selected, along with the variability structure. We first performed a univariate pre-selection based on AIC. A backward procedure from the full model using LRT was then used to select the covariates kept in the final model, with p = 0.1 as the threshold to retain a covariate.

2.6. Model evaluation

Goodness of fit was assessed for each model by plotting population predicted (PRED) and individually predicted (IPRED) concentrations versus observed concentrations (OBS) and by evaluating the residuals by a graphical inspection of the IWRES, PWRES, and normalized prediction distribution errors (NPDE) versus time and predicted concentrations. Individual fits were also inspected. A visual predictive check (VPC) showing the 90% prediction intervals of selected percentiles of the predictions and observations was also performed.

The predicted concentrations were compared with the corresponding observed values using relative bias (mean prediction error or MPE) and precision (root mean squared error or RMSE). The model was considered correctly evaluated if the relative bias and precision were adequate.

$$Meanbias(\%) = 100 \times \left(\frac{\sum PRED - OBS}{N \times OBS}\right)$$

$$Precision(\%) = \frac{100}{OBS} \times \sqrt{\frac{\sum (PRED - OBS)^2}{N}}$$

2.7. External evaluation

The final model was then externally evaluated using 211 additional samples of levofloxacin from the BDDLEVO study (Local ethics committee AP-HP.5, IRB registration # 00011928). Plasma concentrations were predicted by fixing the population parameters in the structural and variance model to the estimates in the final model and using Monolix to estimate the individual parameters. Goodness of fit was verified by plotting the IPREDs against the observed concentrations and evaluating the residuals as described above. The relative bias and precision were also computed for the external dataset.

2.8. Limited sampling strategy (LSS)

Developing a LSS using a Bayesian approach allows using the final model as a clinical tool to accurately predict AUC between doses through a limited number of samples. A Bayesian approach based on the final model was chosen because it allows a change in covariate values, dosing regimen and sampling times, which is essential in a clinical use. Using the final model, we used the Simulx package in R to simulate 1000 plasma concentrations profiles at 0, 0.5, 1, 1.5, 2, 2.5, 3, 3.5 and 4 h. The covariates entering the final model were simulated according to the distribution in the original dataset. Because our objective was to limit the number of samples to 3 samples or less, we then generated datasets including 1, 2 or 3 concentrations among these simulated profile, testing all possible combinations respecting clinical constraints. For each combination of sampling times, we used the model and estimated population parameters to obtain individual Bayesian estimates for each individual in the simulated dataset by fixing the population estimates. We used the estimated clearance to predict the model-based AUC for each subject (AUC_{pred}) and compared it to the AUC computed using the true (simulated) parameters (AUC_{obs}), in both cases using the formula AUC=Dose/CL with the corresponding CL. We then selected the combination of times providing the best agreement between predicted and simulated AUC, as measured by the R^2 adjusted (with an objective of > 90%) and the lowest rate of outliers.

The predictive performance of LSS was also evaluated using bias (MPE) and precision (RMSE). A plot of observed versus predicted concentrations was inspected and a Bland-Altman plot was used to compare AUC_{obs} and AUC_{pred}.

2.9. Probability of target-attainment (PTA)

Monte-Carlo simulations based on the final model were used to evaluate the probability of target attainment (PTA) of different dosing regimens of ofloxacin and levofloxacin. The dosing regimens simulated were 200 mg once daily (QD), 200 mg BID, 300 mg BID and 400 mg BID for ofloxacin and 500 mg QD, 750 mg QD, 500 mg BID and 750 mg BID for levofloxacin to fit the recommended regimens. The target was defined as the probability of 90% of profiles reaching the objective. PTA was evaluated at MICs of 0.125, 0.25, 0.5 and 1 μg/mL. These MICs have been selected because of their clinical relevance and based on the data obtained from EUCAST.

As no clinical target has been validated for ofloxacin or levofloxacin, we used a value of AUC/MIC ratio of 115 h as target [6]. To include the diffusion in bone tissue, which influences therapeutic success in OAI, we also tested 230 h and 383 h as target, corresponding respectively to 50% and 30% bone penetration. These ratios have been derived from values reported in cancellous and cortical bones (54% and 34% respectively) [12].

Simulations and target attainment analysis were performed using the R software and Simulx package.

Table 1
Patient characteristics.

	n (%)	Mean ± SD	Median (min - max)
Samples	297		
Regimen (mg)			
200 BID	19 (63.3)		
200 TID	11 (36.7)		
Age (years)		60.6 ± 16.9	62.5 (23–85)
Weight (kg)		77.2 ± 21.1	72.5 (45–134)
Height (cm)		164.6 ± 10.7	165 (144–185)
BMI (kg/m^2)		28 ± 6.6	28.3 (18.7–40.3)
Sex (male)	16 (53.3)		
LBW (kg)		50.2 ± 13.1	49.3 (31.2–82.1)
BSA (m^2)		1.87 ± 0.29	1.79 (1.39–2.62)
Proteins (g/L)		69.8 ± 7	70 (50–82)
Albumin (g/L)		36.1 ± 4.4	35.9 (24.8–45.7)
Urea (mmol/L)		5.3 ± 2.2	5.2 (2.3–13)
Creatinine (μmol/L)		62.2 ± 20.2	61.5 (29–129)
CKD-EPI (mL/min/1.72 m^2)		96.8 ± 20.8	99.6 (38.9–129.5)
AST (IU/L)		22.7 ± 8.7	21 (11–52)
ALT (IU/L)		22.9 ± 17.4	17.5 (7–91)
Total bilirubin (μmol/L)		8 ± 6.7	6 (2–34)
Conjugated bilirubin (μmol/L)		2.7 ± 3.3	0 (0–10)
ALP (IU/L)		101 ± 46.7	93 (49–270)
GGT (UI/L)		86.9 ± 79	63 (20–398)

BMI: body mass index; LBW: lean body weight; BSA: body surface area; CKD-EPI: chronic kidney disease – epidemiology collaboration; AST: aspartate aminotransferase; ALT: alanine aminotransferase; ALP: alkaline phosphatase; GGT: gamma glutamyl transferase.

Table 2
Pharmacokinetic parameters.

	Mean ± sd	Median (min – max)
Cmin (μg/mL)	2.0 ± 2.0	1.1 (0.6 – 8.3)
Cmax (μg/mL)	4.5 ± 1.9	4.0 (2.2 – 9.1)
Tmax (h)	2.0 ± 1.6	1.3 (0 – 7.0)
CL/F (L/h)	5.4 ± 3.5	6.4 (0.8 – 11.3)
Vd/F (L)	48.7 ± 14.4	49.6 (17.8 – 70.0)
AUC 0–24 h (μg.h/mL)	71.0 ± 43.4	54.2 (30.9 – 195.3)

Cl: clearance; F: bioavailability; Vd = volume of distribution; AUC: area under curve.

3. Results

3.1. Patients and modeling

Thirty patients were included in the study. Their characteristics are presented in Table 1. At the time of the ofloxacin PK profiles, 19 patients were co-treated with rifampin. Eight patients received cloxacillin, 3

Table 3
Significant covariates in univariate selection.

Covariable	P-value for correlation test η-covariable	ΔOFV
Influence on interdividual varibility of V parameter		
BSA	0.011	-8,05
BMI	0.022	-4,14
LBW	0.023	-7,25
Weight	0.005	-7,31
Influence on interdividual varibility of Cl parameter		
BSA	0.028	-9,21
CKD-EPI	< 0.001	-33,19
LBW	0.001	-11,71
Age	0.003	-9,11
Total bilirubin	0.030	-2,37
Height	< 0.001	-16,75
Urea	0.025	-5,96
Sex	< 0.001	-19,22
Influence on interdividual varibility of Ktr parameter		
ALP	0.014	-7,6
Influence on interdividual varibility of Mtt parameter		
Proteins	0.025	-6,28

ΔOFV: objective function difference for the likelihood ratio test (null model – covariate model), significance threshold: $p < 0.01$ or $\Delta OFV < -6.63$; BMI: body mass index; LBW: lean body weight; BSA: body surface area; CKD-EPI: chronic kidney disease – epidemiology collaboration; ALP: alkaline phosphatase; V: apparent central volume; Cl: apparent total clearance; Ktr: transit constant; Mtt: mean transit time.

vancomycin, clindamycin or cefazolin, 2 ceftriaxone or fucidic acid and 1 linezolid. Non-compartmental analysis showed large variations in the PK parameters between patients (Table 2), with trough concentrations (Cmin) ranging from 0.6 to 8.3 mg/L, peak concentrations (Cmax) ranging from 2.2 to 9.1 mg/L and AUC_{0-24} ranging from 30.9 to 195.3 mg.h/L. Coefficients of variations (CV) for these parameters were 102.2%, 43.0% and 61.1%, respectively. The main determinant of the variability seemed to be the drug clearance (CV of 65.7%) rather than the volume of distribution (CV of 29.5%).

Two hundred and ninety-seven (297) ofloxacin concentrations were available for the pharmacokinetic modeling. Ofloxacin PK was best described using a bicompartmental model with a first order elimination, and a transit compartment model absorption. A combined proportional and additive residual error model best fitted the data. Due to a high shrinkage, interindividual variability for the intercompartmental clearance and peripheral volume of distribution were fixed to zero. CKD-EPI and sex had a significant influence on apparent total clearance. Among the 18 covariables tested, CKD-EPI and sex explained half of its variability (Table 3). Results of the multivariate backward model selection with a p-value of 0.1 (a decrease in the objective function of 10.83) were presented in table S1. All the parameters of the final model were estimated with a good accuracy and an acceptable shrinkage (table S2). The final model including covariates for clearance was as follows:

$$CL = 6.67 * \left(\frac{\text{CKD-EPI}}{100}\right)^{1.25} \quad \text{for men}$$

$$CL = 6.67 * \left(\frac{\text{CKD-EPI}}{100}\right)^{1.25} * 1.53 \quad \text{for women}$$

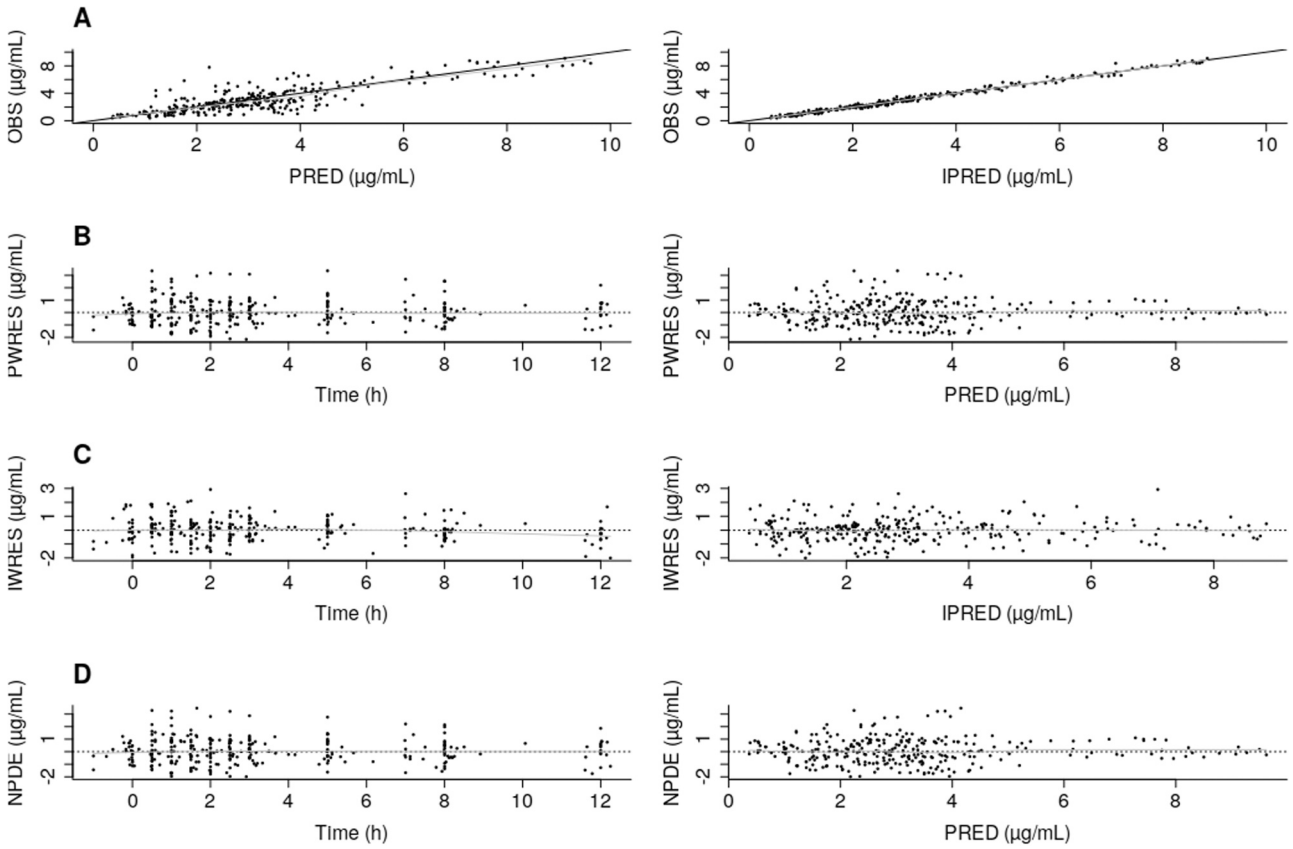


Fig. 1. Model goodness of fit and evaluation for ofloxacin concentration. Observed concentration versus population predicted (PRED) and individually predicted (IPRED) concentrations (A); Population weighted residual (PWRES) versus time, PRED and distributions (B); Individual weighted residual (IWRES) versus time, IPRED and distribution (C); Normalized prediction distribution errors (NPDE) versus time, IPRED and distribution (D).

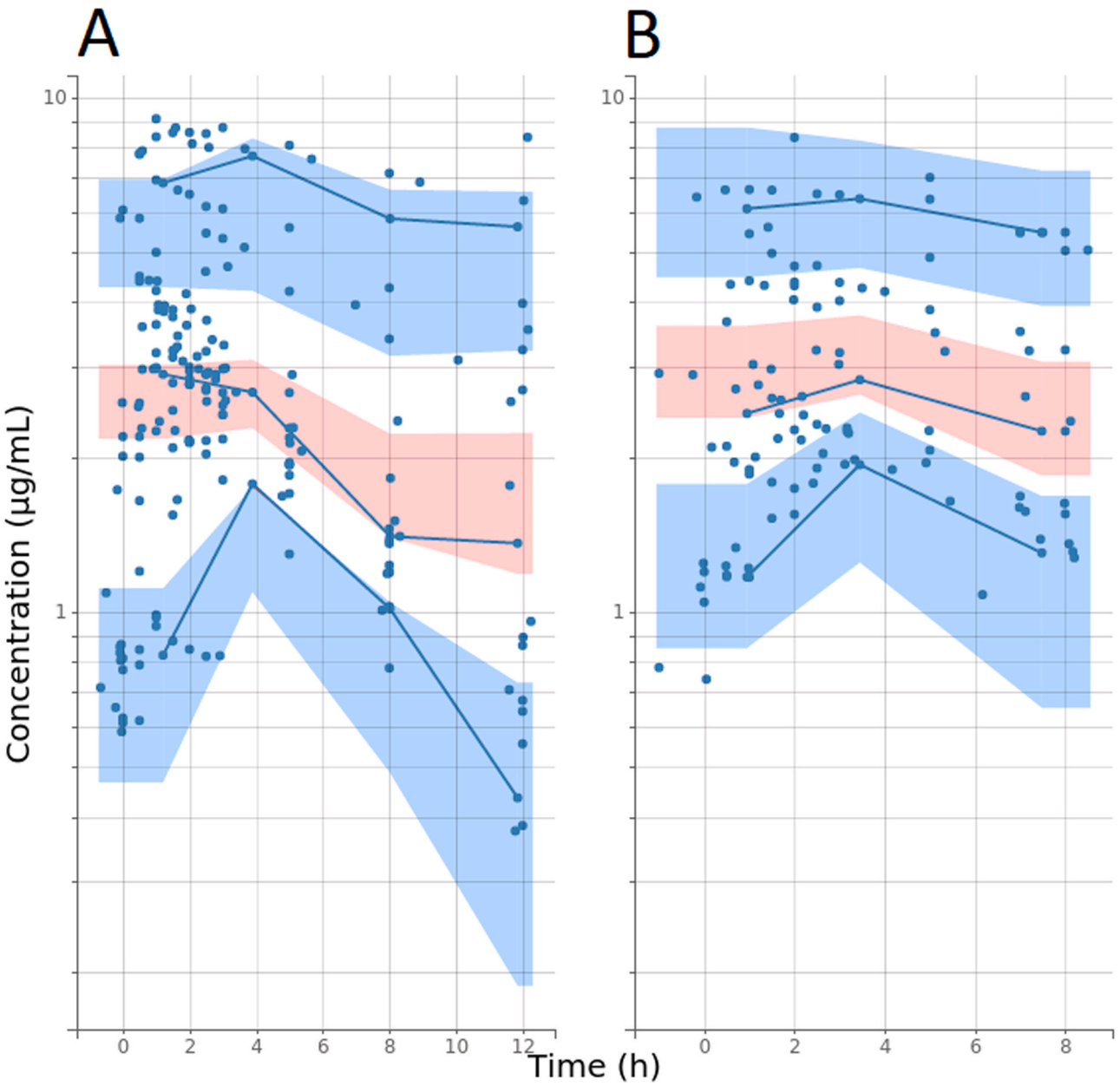


Fig. 2. Visual predictive check (VPC) for ofloxacin concentrations versus time. Observed concentrations are represented by circles and their 10th, 50th, and 90th percentiles with solid lines. The 90% confidence interval of 10th, 50th, and 90th percentiles for predicted concentrations are represented with shaded regions.

3.2. Model evaluation

Graphically, the model appeared adequate with no trend in the distribution of the residuals (Fig. 1). Visual predictive checks for BID and TID regimens showed values within the prediction interval with a slight overestimation of the 10th percentile for the BID regimen (Fig. 2). Best and worst individual adjustments are presented in Fig. S1. We considered that the shrinkage was low enough (<40%) for graphs based on individual predictions to remain informative. The mean relative bias was − 0.12 and − 1.3% for the concentration and AUC values, respectively, and 2.0% and 7.1% for their accuracy.

An external validation was conducted on the independent dataset composed of 211 levofloxacin plasma concentrations measured in OAI patients. Model performance for levofloxacin was good, with mean relative bias and precision for concentrations of − 0.11% and 1.6%, very similar to the values found in the building dataset (Fig. 3).

3.3. LSS determination

For each of the 129 combinations of 1–3 time points, and for each dosage regimen, we estimated the individual parameters using a Bayesian approach and used them to predict the AUC over the dosing interval. The predicted AUC were compared to the simulated AUC using the criteria defined in Methods. None of the schemes with 1 or 2-time points reached the predefined R^2 adjusted objective. For the BID regimen, the best combination of high adjusted R^2 (>90%) and low rate of outliers was obtained for the 0, 1 h an 3 h sampling scheme (R^2 adjusted = 91.1%, outliers = 4.8%) (Fig. S2). For the TID regimen, the best balance was again obtained for the 0, 1 h and 3 h sampling scheme (R^2 adjusted = 95.0%, Outliers = 5.0%) (Fig. S2).

3.4. Probability of target-attainment (PTA) analysis

Simulations were conducted using the final model to evaluate the

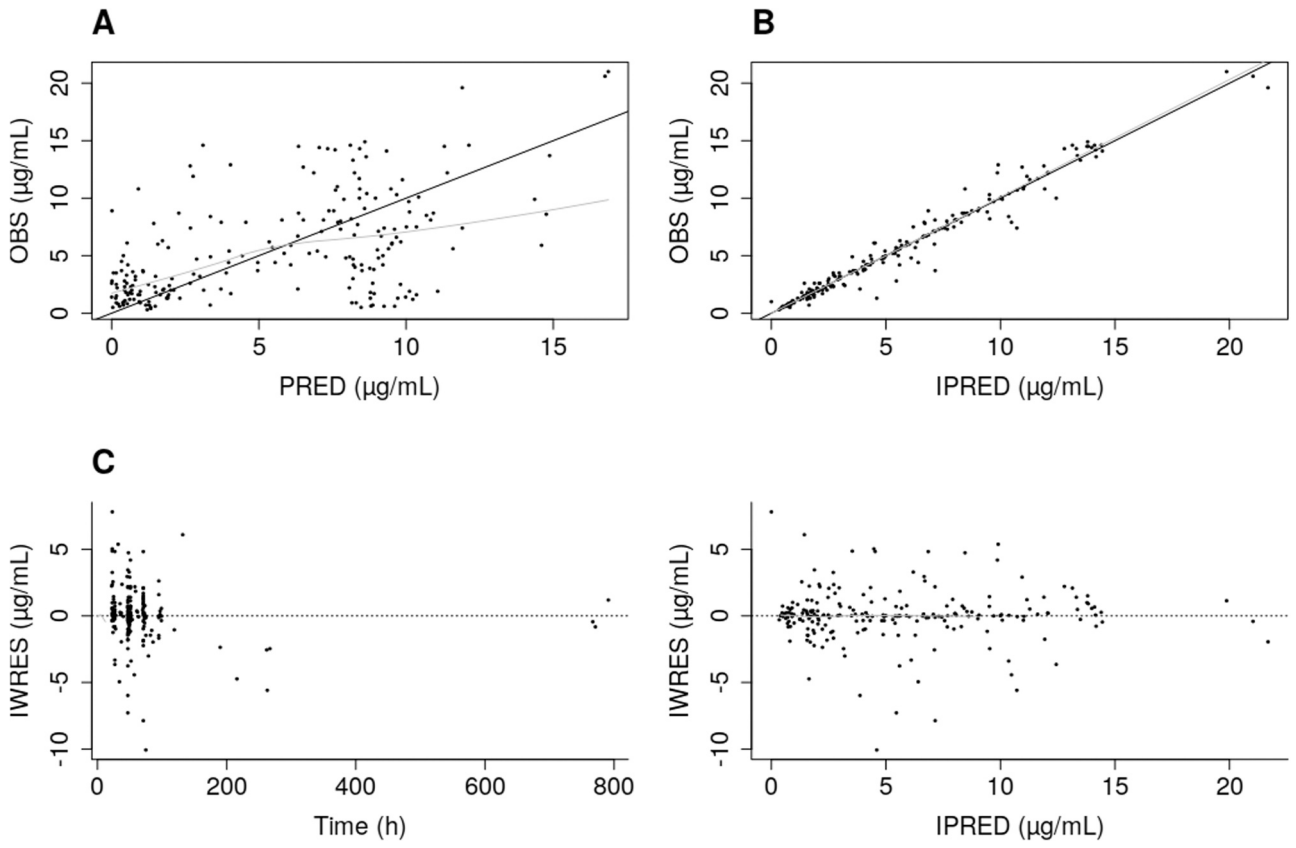


Fig. 3. Model goodness of fit and evaluation for levofloxacin concentration from an external dataset. Observed concentration versus population predicted (PRED) (A) and individually predicted (IPRED) concentrations (B); Absolute individual weighted residuals (|IWRES|) versus Time (C) or IPRED (D).

ability of 4 ofloxacin dosage regimens (200 mg QD, 200 mg BID, 300 mg BID and 400 mg BID) to reach PK/PD target for 4 different MICs and according to 3 hypotheses of bone diffusion (100%, 50% and 30%) (Fig. 4A). For the 100% diffusion hypothesis, the 200 mg BID regimen was associated with a PTA of $\geq$ 90% up to a MIC of 0.25 mg/L while a regimen of 400 mg BID was needed to reach this objective for a MIC of 0.5 mg/L. For the 50% diffusion hypothesis, a dosage of 400 mg BID is required to reach the objective for a MIC of 0.25 mg/L while none of the usual dosage regimens can ensure a sufficient exposure for a MIC of 0.5 mg/L. Finally, when considering a bone diffusion of 30%, a 300 mg BID or 200 mg TID regimen allows reaching a PTA above 80% but only a regimen of 400 mg BID allows reaching a PTA of 90% for a MIC of 0.125 mg/L. With a MIC of 0.25 mg/L, all regimens fail to achieve the target. For the 200 mg QD regimen, a 90% PTA was reached only for a MIC of 0.125 µg/mL. It is noteworthy that, at the EUCAST epidemiological cut-off for *Staphylococcus aureus* (1 mg/L), no ofloxacin dosage regimen generates sufficient exposure to reach the threshold. These results highlighted the difficulty in reaching PK-PD thresholds at the infectious site if the most pessimistic diffusion hypothesis holds.

For levofloxacin, 4 dosage regimens were evaluated (500 mg QD, 750 mg QD, 500 mg BID and 750 mg BID) with the same MICs and bone diffusion hypothesis (Fig. 4B). Assuming the 100% diffusion hypothesis is valid, a 500 mg QD dosage allows reaching the target up to a MIC of 0.25 mg/L while 500 mg BID is required for a MIC of 0.5 mg/L, which is the epidemiological cut-off according to EUCAST for *Staphylococcus aureus*. For a MIC of 1 mg/L, only the 750 mg BID regimen was associated with a 90% PTA. For a bone diffusion of 50%, the 500 mg QD regimen achieves the objective only for a MIC of 0.125 mg/L or less. A 750 mg QD and a 500 mg BID with a higher margin appear to be an adequate regimen for a MIC of 0.25 mg/L while giving patients a 750 mg BID dose of levofloxacin is the only regimen approaching the 90% PTA for a 0.5 mg/L MIC. With a 1 mg/L MIC, no regimen reaches the goal. Finally, when considering a 30% diffusion into bone, a 750 mg QD dosage is required for a 0.125 mg/L MIC and a 750 mg BID dosage is needed for a 0.25 mg/L. Beyond this MIC, no regimen achieves a PTA above 50%.

4. Discussion

In this study, we developed a simple 3 time-points sampling approach to estimate the AUC of ofloxacin and levofloxacin. Population pharmacokinetic models for ofloxacin and/or levofloxacin already exist but they have been established almost exclusively in tuberculosis and respiratory infections [13–17]. To our knowledge, only two studies addressed levofloxacin PK models in bone [18,19]. The first of these studies aimed at evaluating the bone diffusion of levofloxacin in patients who underwent hip or knee arthroplasty, using a commercial modelling software to simultaneously fit plasma and bone concentrations in 42 patients [18]. While the direct measurement of levofloxacin in bone was a key point of that study, patients received a single dose of levofloxacin and the pharmacokinetic sampling scheme was limited to 3 time-points resulting in a one-compartment model with a first order model uptake in bone. The second study aimed at modeling levofloxacin in bone and joint infections to evaluate the current dosage recommendation of 750 mg QD [19]. Glomerular filtration rate estimated through the CKD-EPI formula and age were the two covariates explaining drug clearance variability in that model. As ofloxacin and levofloxacin are mainly renally excreted, renal function is expected to impact drug clearance. Again, because routine data were used in that work, the pharmacokinetic sampling scheme was sparse with only 4 time-points, resulting in a one-compartment model selected, in line with the limited number of samples during the elimination phase. This model was not externally validated which is another difference with our work.

Considering ofloxacin only, two models focused on the drug, both in

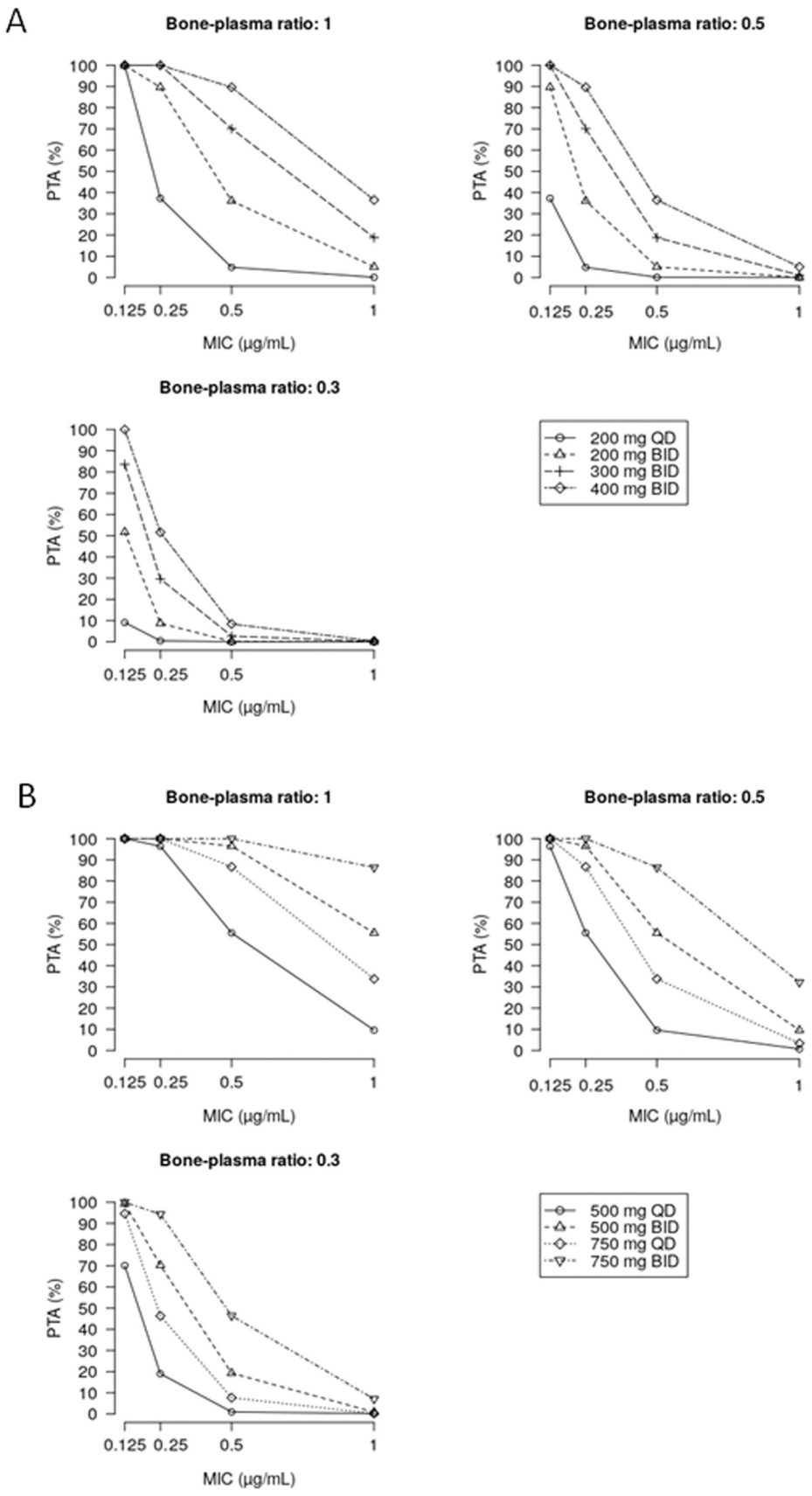


Fig. 4. Probability of target attainment for the different regimens and diffusion in bone tissue (A) for ofloxacin, (B) for levofloxacin.

tuberculosis [14,20].

In our model, we found that glomerular filtration rate estimated with the CKD-EPI formula influences drug clearance, as previously reported [14,20,21]. The other covariate associated with drug clearance was gender. Interestingly, sex is part of the CKD-EPI formula but was also retained independently in the final model.

Overall, only one of the models found in the literature had an external validation set together with the building of a LSS approach [13]. In a study aiming at personalizing levofloxacin dosage in tuberculosis patients, Van den Elsen and colleagues developed a multilinear regression LSS (predose and 4 h postdose) and a Bayesian (predose and 5 h postdose) LSS. Both methods estimated AUCs in agreement with the complete 8 time-points AUC evaluated by a non-compartmental approach (R^2 of 0.966 and 0.821 respectively). In our study, we achieved comparable performance in the OAI population of patients with a 3 time-points Bayesian LSS but a shorter time for sample collection.

The efficacy of fluoroquinolones efficacy is related to the AUC over MIC ratio, as has been demonstrated 27 years ago by Forrest and colleagues [4]. For OAI, the AUC/MIC target is still to be established and we have chosen an elevated target while considering 3 different scenarios for bone diffusion. Despite the lack of a definitive threshold, the PTA part of the study yields practical information for the treatment of OAI. First, the choice of drugs is of importance. Assuming 100% diffusion in bones, ofloxacin can only be used to treat infections with MIC lower or equal to 0.5 mg/L. For a MIC of 0.5 mg/L, only the 400 mg BID dosage regimen ensures sufficient drug exposure. The lowest dosage regimen for ofloxacin (200 mg BID) can be used for MIC of 0.125 mg/L (with a slight decrease of PTA at 0.25 mg/L) while 300 mg BID should be proposed for bacteria with MIC of 0.25 mg/L. Using levofloxacin, 500 mg BID and to a lesser extent 750 mg QD achieve the AUC/MIC target for MIC up to 0.25 mg/L. For bacteria with higher MIC (up to 1 mg/L even beyond the epidemiological cut-off for *S. aureus*), levofloxacin appears as a valuable option but the 750 mg BID dosage should be proposed. A less favorable hypothesis of bone diffusion implies the use of higher fluoroquinolones dosages but still levofloxacin offers better MIC coverage than ofloxacin. However, increasing dosages and drug exposure might be associated with an increase in adverse events (tendinopathy, neurological disorders…).

Hence, for 50% bone diffusion, standard dosage regimen allows approaching AUC/MIC target for MICs of 0.25 mg/L with levofloxacin 750 mg QD while ofloxacin 200 mg BID is suitable only for MIC up to 0.125 mg/L. For a MIC of 0.25 mg/L, target can still be reached with an ofloxacin dosage of 400 mg BID.

Finally, considering a 30% bone diffusion, the highest drug dosage allows better coverage for levofloxacin (up to MICs of 0.25 mg/L) than for ofloxacin (up to MICs of 0.125 mg/L).

Regarding the limitations of this study, the AUC/MIC ratio used for the simulation has not been validated for OAI but was based on specific experiments on *Staphylococcus* sp.. infections and was in line with other clinical studies [15,21]. Another key limitation point is the inability to elicit specific bone:plasma diffusion ratio for ofloxacin and levofloxacin because data are not univocal, ranging from 0.09 to 1.8 [22]. We choose our bone:plasma diffusion ratios hypothesis based on concurring data reported for ofloxacin and levofloxacin with lower ratios found for cortical bone while diffusion in cancellous bone is reported to range from 50% to 100% [12,23,24]. In absence of any definitive conclusion, the choice of target should be driven by infection location and according to the clinical settings. Finally, the complete sampling scheme while being limited to 3 h can be seen as a long stay in the outpatient phase of infection management but this relatively time-consuming approach has to be balanced with the benefit of maximizing efficacy and minimizing the risk of adverse events onset by individually adjusting FQs to AUC/MIC ratio.

One important advantage of our model is its robustness, demonstrated by the external validation on a separate dataset, and its ability to offer a convenient tool for both ofloxacin and levofloxacin treatments. Evaluating AUC also offers the possibility to decrease the rate of adverse drug reactions particularly for those potentially associated with drug accumulation (arthropathy, tendinitis, cardiac rhythm disorder and neurological adverse events). Finally, this model can now be used prospectively to establish a definitive AUC/MIC target in the field of OAI treatment.

5. Conclusion

An evaluation of ofloxacin and levofloxacin exposures is required for appropriate therapeutic drug monitoring in osteoarticular infections to limit the risk of treatment failure and decrease the rate of adverse drug reactions. We developed a simple 3-sample protocol (pre-dose, 1 h after intake and 3 h after intake) to estimate the AUC of these fluoroquinolones allowing optimal drug dosage for the treatment of OAI.

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CRediT authorship contribution statement

FL: designed the research, performed the research, wrote the manuscript; FF, MR, PT, CA, VJ, CT, MCV, JLP, DH: performed the research; JBF, AP: analyzed the data; EC: analyzed the data, wrote the manuscript; EB, BL: designed the research, performed the research, wrote the manuscript.

Conflicts of interest statement

All authors declare that they have no conflict of interest.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.biopha.2021.112053.

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