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ORIGINAL ARTICLE

Population pharmacokinetic modelling of prednisolone in systemic lupus erythematosus patients: Analysis of exposure and disease activity

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Abstract

Aims: Prednisone is a widely used glucocorticoid in the treatment of lupus, although its dosing is often determined empirically. Prednisolone, the active metabolite of prednisone, is found in its free form in the serum. The goal of this study was to develop a population pharmacokinetic model in patients with systemic lupus erythematosus (SLE) to forecast free prednisolone concentrations and its association with disease activity.

Methods: A total of 66 active SLE patients (adults and children) were included, and followed up prospectively (242 observations available). Plasma prednisolone concentrations were assessed using liquid chromatography-mass spectrometry, and the data were analysed using Monolix software. The pharmacokinetic model was a one-compartment open model with absorption lag time representing the delay for both absorption and metabolism from inactive (prednisone) to active form (prednisolone). This model predicted free concentrations, which were then used to calculate total concentrations based on established binding constants.

Results: Free prednisolone clearance (CLu/F) and volume of distribution (Vu/F) were scaled allometrically to body weight. The typical population estimates (95% confidence interval) were 54 (48–62) L/h/70 kg and 235 (203–274) L/70 kg, respectively.

The authors confirm that the Principal Investigator for this paper is Brigitte Bader-Meunier and that she had direct clinical responsibility for patients.

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Additionally, the bioavailability parameter was found to decrease non-linearly with the dose. Prednisolone cumulative exposure was not different between patients who responded at 3 months and those who did not.

Conclusions: Robust pharmacokinetic targets are not yet clearly defined regarding toxicity or efficacy and are warranted in order to make a valuable contribution to prednisolone therapeutic drug monitoring in the context of SLE.

KEYWORDS
population pharmacokinetics, disease activity

1 | INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease that can lead to severe multiple organ damage and increases the incidence of early atherosclerosis by a factor of nine to 50.[1] Until now, glucocorticoids have played a central role in the treatment of lupus, significantly improving prognosis, especially during severe flare-ups when combined with immunosuppressants such as **mycophenolate mofetil** (MMF) and **hydroxychloroquine**. This approach has improved 10-year survival rates to 70–90%.[2] However, corticosteroid treatment remains a major cause of morbidity and mortality both in paediatric and adult patients with SLE, and despite 60 years of experience, there is still no consensus on optimal dosages, routes of administration and tapering regimens.

Furthermore, there is substantial variability in clinical response to corticosteroid therapy, likely due to the heterogeneity of SLE, drug absorption and interactions, and environmental or genetic factors.[3] Previous studies, particularly in renal transplant populations, have demonstrated relationships between **prednisolone** pharmacokinetics (PK) and clinical efficacy/toxicity.[4–6] In SLE patients, only two small series (8 children, 25 adults) have explored these relationships, suggesting that SLE activity or corticosteroid toxicity might be linked to prednisolone area under the curve (AUC).[3,7] However, limited evidence indicates that monitoring **prednisone** levels could optimize treatment efficacy and reduce adverse events.

Variability may manifest at various stages of prednisone's complex pharmacokinetics. After a significant intestinal absorption (62%–95%),[8,9] prednisone undergoes a first-pass effect in the liver, where it is metabolized to prednisolone by **11-β Hydroxysteroid dehydrogenase**. Both prednisone and prednisolone bind to corticosteroid-binding globulin (CBG) and albumin. CBG exhibits high affinity but low capacity for prednisolone, while albumin has low affinity but high capacity. Protein binding is significant because only free prednisolone acts on glucocorticoid receptors[10] and is either excreted unchanged by the kidney (20%) or inactivated by liver enzymes (80%).[11,12]

The goal of this study was to develop a population pharmacokinetic (PK) model in patients with SLE to forecast free prednisolone concentrations and its association with disease activity.

What is already known about this subject

- Glucocorticoids have played a central role in the treatment of systemic lupus erythematosus (SLE), significantly improving prognosis, especially during severe flare-ups.
- There is substantial variability in clinical response to corticosteroid therapy, likely due to the heterogeneity of SLE, variability in drug pharmacokinetics and environmental or genetic factors.
- Limited evidence indicates that monitoring prednisone levels could optimize treatment efficacy and reduce adverse events.

What this study adds

- Cumulative exposure to prednisolone was not significantly different between responders and non-responders after three months of treatment, suggesting that increasing prednisone doses beyond a certain level does not enhance clinical outcomes.
- Prednisolone bioavailability appears to decrease as prednisone doses increase, meaning that increasing prednisone doses beyond a certain point may not improve the effective exposure to prednisolone.
- Our data support practical guidelines which advise limiting prednisone doses to a maximum of 30–60 mg/day for lupus patients and tapering off prednisone as soon as disease control is achieved.

2 | METHODS

2.1 | Study design and participants

The study was approved by the local ethics committee (Comité de Protection des Personnes, SUD-EST IV, No. EUDRACT:

2017-002050-36) and registered in the clinicaltrials.gov database under the reference NCT03187743. This was a prospective, observational, multicentre study. Patients were enrolled from 28 French paediatric and adult centres at university hospitals. Consecutive patients receiving oral prednisone for active SLE disease were enrolled between April 2018 and January 2022. The clinical care of the patients was not modified by the study. The regimen for standard of care was based on the patient's disease manifestations and was in accordance with the investigators' approach to standard treatment for those disease signs and symptoms. The main inclusion criteria were: (1) patients aged ≥ 6 years; (2) patients who met the American College of Rheumatology criteria (ACR) or the Systemic Lupus International Collaborating Clinics Classification (SLICC) for systemic lupus erythematosus; (3) initiation of oral prednisone regimen at least at 0.5 mg/kg/day in combination or not with mycophenolate mofetil or mycofenolic acid or cyclophosphamide at usual dose, including (i) patients who received bolus of methylprednisolone the week before and/or the week after inclusion for treating the lupus flare, (ii) patients who were previously treated by a low-prednisone dose (≤ 7.5 mg/day in patients ≥ 60 kg and ≤ 0.1 mg/kg/day in patients < 60 kg), (iii) patients who were previously treated by prednisone ≥ 0.5 mg/kg/day (or > 30 mg/day for patients > 60 kg) but stopped for at least 1 month before inclusion; (iv) patients with stable doses of other immunosuppressive or biological drugs before inclusion (at least 15 days for azathioprine, methotrexate, tacrolimus; at least 6 months for rituximab, belimumab) and during the 3 months of patient participation in the study. The prednisone dose to be evaluated was ≥ 0.5 mg/kg/day, but the precise dosage and the tapering regimen was determined according to the clinical judgement of the investigators.

The duration of the research period for each patient was 3 months. Three visits (which are all usual care visits) were planned for collecting data and/or blood sampling. The first visit was the inclusion visit, followed by two follow-up visits at 1 and 3 months respectively. The first day of treatment with prednisone ≥ 0.5 mg/kg/day was considered as Day 0 of the study. Prednisone was administered orally according to the usual practices of the corresponding centres. Score of disease activity (SELENA-SLEDAI) was collected at each visit. PK samples were collected for the study by venipuncture during routine biological monitoring performed at study follow-up visits (inclusion visit, and at 1 and 3 months). The delay between drug intake and blood sampling was assigned randomly as part of routine care. No venous or arterial puncture was performed specifically for the protocol.

2.2 | Methods and measurements

Clinical information was prospectively collected from the electronic health records. Blood samples drawn for biological analyses were used for drug determination. Plasma was separated by centrifugation and stored at −80 °C until analysis. Total prednisolone was assayed using liquid chromatography coupled with tandem mass spectrometry (LC–MS/MS; Waters®, Milford, USA). In the reported procedures, prednisolone-d6 was used as the internal standard (IS). For sample preparation, 200 µL of plasma samples and 10 µL of internal standard solution were mixed with 1.5 mL of ethyl acetate. After centrifugation, the supernatant was evaporated to dryness and reconstituted with 100 µL of mobile phase. Finally, 20 µL of each sample was injected into the chromatographic system. An Acquity UPLC® chromatography system (Waters®, Milford, USA) piloted by Masslynx software (version 4.1) was used in this method. The separation was carried out on a KINETEX XB-C18 analytical column (50 × 2.1 mm, 1.7 µm; Waters®, Milford, USA). The mobile phase consisted of water (0.05% formic acid, v/v; A) and methanol (0.05% formic acid, v/v; B). The analytes were eluted using a linear gradient over 10 min. Detection was performed using a Xevo TQD triple-quadrupole mass spectrometer (Waters®, Milford, USA) with a heated electrospray ionization (H-ESI) ion source. Prednisolone and prednisolone-d6 were analysed in the positive multiple reaction monitoring (MRM) scan mode. The following transitions for quantification were monitored: m/z 361.1 > 147.1 for prednisolone and m/z 367.1 > 349.24 for prednisolone-d6. The method was linear in the range of 5–500 ng/mL. The intraday and interday accuracy ranged from 0.3% to 6.8%, and the intraday and interday precision ranged from 3.5% to 7.1%.

2.3 | Pharmacokinetic modelling

Data were analysed using the non-linear mixed-effects modelling software program Monolix version 2023R1 (http://lixoft.com). Parameters were estimated using the Markov Chain Monte Carlo-Stochastic Approximation Expectation Maximization algorithm (MCMC-SAEM). Various structural models were tested to describe prednisolone concentrations, including one- or two-compartment models, first-order absorption with potential delays, and first-order elimination.

In previous studies, non-linear (saturable) binding between corticosteroid binding globulin (CBG) and prednisolone was observed depending on the available binding sites.[13] A model that accounted for non-linear total prednisolone pharmacokinetics due to saturable, high-affinity plasma protein binding was also evaluated as follows:

$$C_{tot} = CU^{*}\{1 + B_{max}/(1 + K_1{}^{*}\,CU) + K_{ns}\}$$

where CU and C_{tot} are unbound and total drug concentrations, respectively; K_1 and B_{max} represent the affinity constant and binding capacity for CBG, respectively; and K_{ns} denotes the linear, non-saturable binding constant for albumin. B_{max}, K_1 and K_{ns} values were set according to Petersen et al.[14]

Between-subject variabilities (BSV) were modelled exponentially. For residual variability, proportional, additive and combined error models were considered. Data below the limit of quantification (BLQ) were managed as left-censored data by MONOLIX.

Model fitting and comparisons were based on the change in objective function value (OFV) for nested models, and on the Bayesian Information Criterion (BIC) for non-nested models.

Potential covariates influencing prednisolone pharmacokinetics included age, sex, weight, height, serum creatinine, creatinine clearance (eGFR), estimated using the MDRD formula for patients 18 years or older and using the Schwartz formula for patients younger than 18 years old, and liver enzymes (aspartate aminotransferase [AST], alanine aminotransferase [ALT] and gamma-glutamyl transferase [gamma GT]). Allometric rule was used for testing total bodyweight in the covariate model with power exponents fixed to 0.75 and 1 for CL and V, respectively.[15]

Continuous covariates (COV) were evaluated using the following equation, with clearance (CL) as an example:

$$CL = \theta_{CL} \times \left(\frac{COV}{median(COV)}\right)^{\beta_{COV}^{CL}},$$

where θ_{CL} is the typical value of clearance for a patient with the median covariate value and β_{COV}^{CL} is the estimated influential factor for the continuous covariate.

Binary covariates (CAT) were assessed as follows:

$$CL = \theta_{CL} \times (\beta_{CAT}^{CL})^{CAT},$$

where β_{CAT}^{CL} is the estimated impact factor for the binary covariate, CAT = 0 corresponds to the reference θ_{CL}, and CAT = 1 in the presence of the covariate.

Model quality was assessed by visually inspecting observed *vs.* predicted (population and individual) concentration scatter plots. Diagnostic graphics and other statistics were obtained using R software (http://www.r-project.org). From the final model, prediction corrected visual predictive check (VPC) and the normalized prediction distribution error (NPDE) metrics were computed. Bayesian estimation was used to derive individual pharmacokinetic parameter estimates from the final model.

2.4 | Clinical outcomes analyses

The primary assessment criterion was SLE disease activity at Month 3 (M3) using the SELENA-SLEDAI flare composite score (range 0–105, with 0 indicating inactive disease). The responders were defined as patients with no flares according to SELENA-SLEDAI score. The SELENA-SLEDAI score allows the definition of either mild/moderate flare or severe flare. Patients with a flare of any severity at one of the two follow-up visits were considered to have active SLE.[16] Mild or moderate flares were defined by one or several of the following: (i) change in SLEDAI instrument score to >3; or (ii) new/worse: SLE skin disease, nasopharyngeal ulcers, pleuritis, pericarditis, arthritis, fever (SLE); or (iii) increase in prednisone, < 0.5 mg/kg/day); or (iv) added non-steroidal anti-inflammatory disease or hydroxychloroquine for SLE disease activity; or (v) ≥1.0 increase in the Physician's Global Assessment (PGA) score, but not to more than 2.5. Severe flares were defined by one or several of the following: (i) change in SELENA-SLEDAI instrument score to >12; or (ii) new/worse:, CNS-SLE, vasculitis, platelet count <60 000; haemolytic anaemia: Hb < 70 g/L or decrease in Hb > 30 g/L) requiring: double prednisone, or prednisone increase to >0.5 mg/kg/day (if it occurs between two consecutive visits of the protocol); or (iii) hospitalization for SLE activity; or (iv) increase in prednisone > 0.5 mg/kg/day; or (v) new cyclophosphamide, azathioprine, methotrexate for SLE activity; or (vi) increase in the PGA score >2.5.

The cumulative area under the curve from 0 to 3 months (AUC0-M3) (accounting for all dose modifications during the patient's follow-up) was derived using the Bayesian estimation approach from the population pharmacokinetic model. Both total and predicted free prednisolone concentrations were considered. The individual exposures were compared between responders and non-responders using a Wilcoxon test. Multivariable logistic regression was also performed in order to account for confounding factors. The following variables were firstly assessed in univariate analysis: age, methylprednisolone bolus administrations, concomitant drugs including immunosuppressors and other biological parameters. Thereafter, the variables with $P < 0.1$ were entered into the multivariable logistic regression analysis (provided there was a minimum of five patients per level for the categorical variables).

Occurrence of adverse events related to prednisone according to the investigator's judgement during the 3-month period follow-up were also investigated. Adverse events of special interest were: increased appetite, Cushing's Syndrome including hirsutism or acne, sleep disorders and psychiatric disorders (mood changing: excitation, sadness, aggressiveness, stress). Time-dependent covariates in a Cox proportional-hazards regression model was performed for adverse events data analysis. Daily AUCs throughout follow-up ($AUC_{0\text{-}24h}$) were derived for each patient and were considered as a time-dependent covariate. Daily AUCs used in the analysis were based on both total and unbound concentrations. Association between log transformed $AUC_{0\text{-}24h}$ and instantaneous rate of adverse event occurrence over time was assessed using hazard ratio estimates along with their 95% confidence interval.

2.5 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY, and are permanently archived in the Concise Guide to PHARMACOLOGY 2019/20.[17]

3 | RESULTS

3.1 | Population characteristics, prednisolone sampling and concentrations

A total of 66 patients (34 patients with juvenile SLE and 32 patients with adult-onset SLE) and 242 observations were available for

analysis. Baseline characteristics of patients are displayed in Table 1. Blood sampling was performed between 5 min and 32 h after the last prednisone administration (median 3.3 h, interquartile range [2 h–6.5 h]). The median number of observations available per patient was 3 and ranged from 1 to 11. There were 35 BLQ concentrations (14% of samples).

TABLE 1 Subject characteristics ($n = 66$).

Variable	
Systemic lupus erythematosus	
Newly diagnosed	34 (51.5%)
In relapse	32 (48.5%)
Type of SLE flare	
Cutaneous	35 (53.0%)
Buccal	15 (22.7%)
Articular	32 (48.5%)
Renal	49 (74.2%)
Pulmonary	9 (13.6%)
Cardiac	15 (22.7%)
Haematologic	31 (47.0%)
Neurologic	16 (24.2%)
Prednisone dose at initiation, mg/kg/day	0.94 [0.65, 1.06] (0.38, 2.3)
Age, year	23 [14.2, 31.2] (6, 63)
Sex	
Male	13 (19.7%)
Female	53 (80.3%)
Bodyweight, kg	56.1 [46.8, 66.5] (17.3, 113.5)
Height, cm	162 [155, 168] (116, 180)
Ethnicity	
Caucasian	19 (29.2%)
North African	10 (15.4%)
Turkish	1 (1.5%)
Asian	13 (20.0%)
Sub-Saharan African	12 (18.5%)
Central/South American	1 (1.5%)
Caribbean	7 (10.8%)
Mixed	2 (3.1%)
Methylprednisolone bolus administrations	38 (57.6%)
Mycophenolate mofetil	35 (53.0%)
Hydroxychloroquine	58 (87.9%)
Leucocytes, 10^9L	7 [4.7, 10.2] (2.3, 24.6)
AST, UI/L	26 [18.8, 40.5] (13, 193)
ALT, UI/L	26 [15, 40] (5, 230)
Gamma GT, UI/L	32 [18, 60] (10, 597)
Alkaline phosphatase, UI/L	73 [54.8, 88.5] (34, 211)
Creatinine, µmol/L	65 [51, 87] (24, 245)
eGFR, ml/min	100.8 [68.4, 122.1] (19.2, 238)
Albuminaemia, g/L	30.5 [24.0, 34.6] (14.9, 43.9)
Proteinuria, g/L	0.71 [0.27, 2.2] (0, 11.2)
Creatinuria, mg/l	734.5 [510.7, 1208.5] (2.5, 2267.8)

Note: Continuous data are given as median [interquartile range] and (range), eGFR estimated glomerular filtration rate by Schwartz and MDRD formula for paediatric and adult patients, respectively.

3.2 | Population pharmacokinetic modelling

A one-compartment model satisfactorily described the prednisolone PK data. The addition of a lag time in the absorption phase improved further the model and resulted in a nine-unit drop in the OFV. Thereafter, a model that accounted for non-linear total prednisolone pharmacokinetics due to saturable, high-affinity plasma protein binding was added. This caused a 55-unit drop in the BIC and substantially improved the curve-fitting. Body weight effect on both clearance and volume parameters (through allometric scaling) was found to be significant (31-unit drop in the OFV). An additional effect of administered dose at the time of observation was also pointed out on prednisolone bioavailability by a 14-unit drop in the OFV ($P = 0.0002$). No other additional covariates resulted in a significant decrease in the OFV. A correlation plot of covariates assessed in the population pharmacokinetic modelling is provided in Supplemental data file S1. Table 2 summarizes the final population pharmacokinetic estimates. The parameters were well estimated with low relative standard errors. The prediction-corrected visual predictive check shows that the median of observed data is well within the 90% confidence interval of the simulated data (Figure 1). Monolix code of the final model and goodness-of-fit plots are provided in supplemental data files S2 and S3, respectively. The BLQ predictive check plot is provided in supplemental data file S4.

3.3 | Clinical outcomes analyses

At 3 months, 53 patients were responders (80.3%), while 13 (19.7%) still had active SLE. As shown in Figure 2, no difference in cumulative free or total prednisolone $AUC_{0\text{-}M3}$ was observed between responders and non-responders ($P = 0.89$ and $P = 0.77$ for total and free drug, respectively). A univariate analysis of factors associated with clinical response is provided in Table 3. Among the variables analysed, ethnicity showed a statistically significant difference between responders and non-responders ($P = 0.007$). Specifically, a higher proportion of responders were Caucasian (34.6%) compared to non-responders (7.7%), while differences were less pronounced for other ethnic groups. No significant differences were observed for age, height or bodyweight. Similarly, the type and the status of SLE (newly diagnosed or in relapse) did not differ significantly between the two groups. Leucocyte count and AST baseline levels approached statistical significance ($P = 0.061$ and $P = 0.073$, respectively). In multivariable analysis, the best positive predictors of clinical success were both the leucocyte levels at baseline (OR [95%CI] per 1-unit increase, 1.7 [1.04–2.3]) and hydroxychloroquine use (OR 7.9 [1.2–50]). Otherwise, elevated aspartate aminotransferase (AST) level at baseline was associated with higher probability of clinical failure ($P = 0.013$).

Regarding occurrence of adverse events, 30/66 patients (45.5%) experienced adverse events related to prednisone during the 3-month follow-up period: sleep disorders for 23 patients (34.8%), psychiatric disorders for 19 patients (28.8%), increased appetite for eight patients (12.1%) and Cushing's Syndrome including hirsutism or acne was reported for six patients (9.1%). No serious infection was reported in this study. Event-free probability as a function of time is provided in Figure 3. No association between daily-predicted free or total prednisolone AUC and adverse event risk was found (Table 4).

TABLE 2 Parameter estimates of the final prednisolone population model.

Parameter	Covariate effect	Estimate (% rse)
T_{lag} (h)	-	0.17 (2)
k_a (h^{-1})	-	1.19 (1)
F	$(Dose/80000)^{\beta_{Fdose}}$	1*
β_{Fdose}	-	−0.28 (2)
CL_U/F ($L.h^{-1}.70\ kg^{-1}$)	$(BW/70)^{0.75}$	54.3 (7)
V_U/F ($L.70\ kg^{-1}$)	$(BW/70)^{1}$	235 (8)
B_{max}	-	6.77*
K_1 (L/nmol)	-	0.0095*
K_{ns}	-	0.8*
$\omega_{CL,U}$	-	0.35 (17)
ω_{Bmx}	-	0.3*
Residual variability, proportional	-	0.42 (7)

Note: % rse, percent relative standard error; ω, between-subject variability; F, bioavailability; Dose, prednisone dose in nmol; β_{Fdose}, dose effect on bioavailability (as an indication, 80 000 nmol corresponds to 30 mg of prednisone); CL_U, clearance of unbound prednisolone; V_U central volumes of distribution of unbound prednisolone; * fixed value.

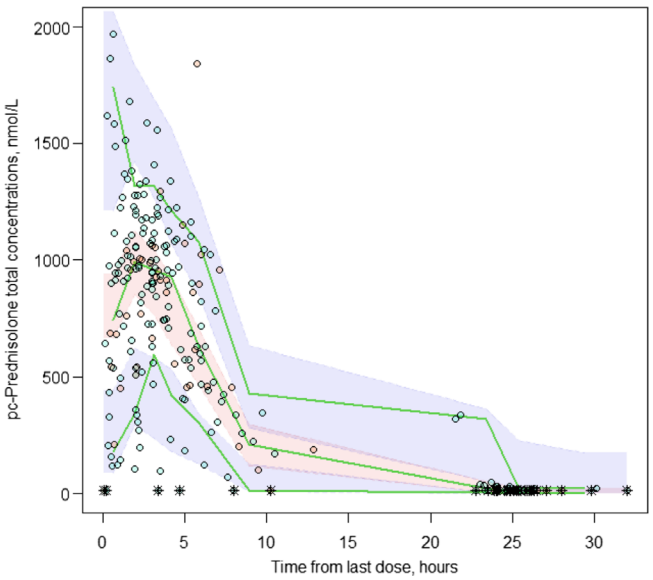

FIGURE 1 Prediction corrected visual predictive check (pcVPC). The lines show the 10th, 50th and 90th percentiles of observed data. The areas represent the 90% confidence interval around the simulated percentiles. Light-blue filled circles stand for pc-observed prednisolone concentrations in responder patients, light-red filled circles stand for pc-observed prednisolone concentrations in non-responder patients and stars stand for below limit of quantification data.

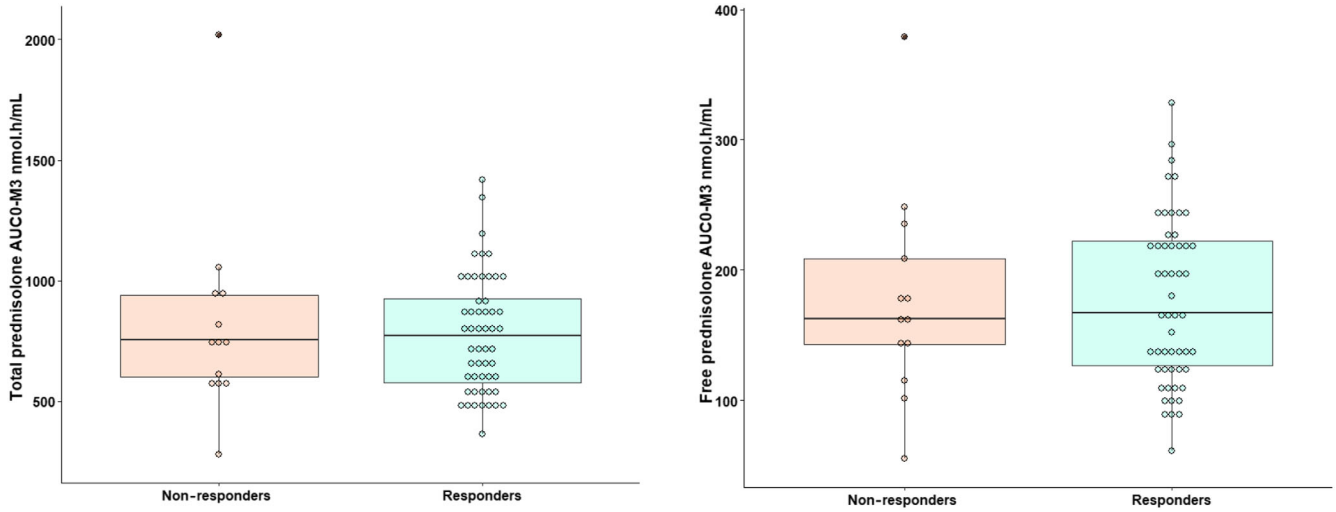

FIGURE 2 Cumulative total (left) and free (right) prednisolone $AUC_{0\text{-}M3}$ between the responders and non-responders.

4 | DISCUSSION

This study is the first to assess prospectively the pharmacokinetics of prednisone based on compartmental analysis in a large cohort of paediatric and adult patients with active SLE requiring initiation of oral high-dose corticosteroid treatment (≥ 0.5 mg/kg/day). The plasma protein binding of prednisolone exhibits non-linear behaviour, requiring the assessment of free concentrations to linearize its pharmacokinetics. The model applied in this study used free concentrations derived from established binding constants and improved significantly the fit. The use of a high range of doses of prednisone in this cohort allowed us to point out a dose effect on the prednisolone bioavailability, adding to the non-linearity of its pharmacokinetics. The dose dependency in prednisolone PK appears to be partially explained by changes in protein binding and other mechanisms are likely to contribute. While distribution volume and clearance are typically considered independent pharmacokinetic parameters, this distinction may not fully apply to prednisolone. Prednisolone undergoes biotransformation in multiple tissues, including the liver, lung, kidney and skin.[18–20] At higher doses, a larger fraction of the drug may distribute to tissues with higher metabolic activity. Additionally, dose-dependent physiological effects of corticosteroids may play a role. For instance, prednisolone has been associated with increased renal blood flow in animal studies.[21] This effect may be particularly relevant at higher doses. Otherwise, prednisone appears to be primarily absorbed through passive diffusion in the gastrointestinal tract, but at higher doses, the dissolution rate or the available absorptive surface area could become limiting factors.

Several points show the relevance of the binding model that was used. Beyond the improvement in fit, evidenced by the significant decrease in the BIC after adding this binding component to the model, the most significant argument is the estimate of CLu found in the present study that, after scaling to equivalent prednisone dose, aligns with values reported in previous population PK analyses performed in other disease conditions[22,23] (i.e, 41 L/h and 37 L/h, respectively). Garg and Jusko[8] measured the unbound prednisolone concentration in 12 subjects following a high oral prednisone dose of 0.8 mg/kg (mean: 63.5 mg), which closely aligns with our study design. The unbound clearance (CL) in their study, calculated from the reported free prednisolone AUC, was 86 L/h. This value is comparable to the 75 L/h predicted by our model for a typical 80 kg patient (mean body weight reported in Garg and Jusko) receiving a 63.5 mg prednisone dose.

Interindividual variability in prednisolone pharmacokinetics was explained mainly by total bodyweight. Prednisolone pharmacokinetics was not linear with total bodyweight but followed an allometric rule. The allometric model enable the extrapolation of the pharmacokinetics parameters from adult to child, through the standardization of results and it also account for the heterogeneity of weight within a population.[15] Therefore, considering an allometric relationship, a simple dose per kg adaptation may result in underdosing in the youngest and in overdosing in the heaviest with possible increased rate of failure or adverse effects. Other factors were reported to influence prednisolone PK in the literature. A sex effect was reported on serum concentration of corticosteroid-binding globulin with women exhibiting a 20% higher level compared to men.[24] However, our study did not indicate a sex effect on prednisolone pharmacokinetics parameters suggesting a minor PK impact of the corticosteroid-binding globulin level variations between sexes. Renal function has also been reported to be associated with prednisolone clearance with a 54% increase in free prednisolone AUC in patients with end-stage renal failure compared to healthy controls.[25] In our study, estimated glomerular filtration rate was not significantly associated with prednisolone clearance, but only two patient had an eGFR< 30 mL/min. Additionally, no patients in our study had dysthyroidism, which has been described to alter prednisolone clearance.[26,27] The variability in clinical response to corticosteroid therapy might be attributed to genetic factors, especially to polymorphism of the multi-drug

TABLE 3 Univariate analysis of baseline characteristics associated with clinical response at 3 months.

	Level	Non-responders ($n = 13$)	Responders ($n = 53$)	*P*-value
Systemic lupus erythematosus	Newly diagnosed	7 (53.8%)	27 (50.9%)	
	In relapse	6 (46.2%)	26 (49.1%)	0.99
Type of SLE flare	Cutaneous	8 (61.5%)	27 (50.9%)	0.71
	Buccal	4 (30.8%)	11 (20.8%)	0.47
	Articular	5 (38.5%)	27 (50.9%)	0.62
	Renal	10 (76.9%)	39 (73.6%)	0.99
	Pulmonary	3 (23.1%)	6 (11.3%)	0.36
	Cardiac	3 (23.1%)	12 (22.6%)	0.99
	Hematologic	6 (46.2%)	25 (47.2%)	0.99
	Neurologic	2 (15.4%)	14 (26.4%)	0.50
Age, year		23 [15, 35]	23 [14, 29]	0.96
Sex	Male	2 (15.4%)	11 (20.8%)	
	Female	11 (84.6%)	42 (79.2%)	0.99
Height, cm		164 [156, 169]	162 [155, 168]	0.44
Bodyweight, kg		60.4 [46.7, 68.4]	53.5 [47, 61]	0.42
Ethnicity	Caucasian	1 (7.7%)	18 (34.6%)	0.007
	North African	3 (23.1%)	7 (13.5%)	
	Turkish	0 (0.0%)	1 (1.9%)	
	Asian	1 (7.7%)	12 (23.1%)	
	Sub-Saharan African	2 (15.4%)	10 (19.2%)	
	Central/South American	0 (0.0%)	1 (1.9%)	
	Caribbean	4 (30.8%)	3 (5.8%)	
	Mixed	2 (15.4%)	0 (0.0%)	
Methylprednisolone bolus administrations		6 (46.2%)	32 (60.4%)	0.54
Mycophenolate mofetil		6 (46.2%)	29 (54.7%)	0.81
Hydroxychloroquine		9 (69.2%)	49 (92.5%)	0.042
Leucocytes, 10^9 L		5.6 [3.3, 7.9]	7.5 [5.6, 10.7]	0.061
AST, UI/L		36 [24, 117]	24 [17.5, 36.5]	0.073
ALT, UI/L		26 [16, 74]	24.5 [14.8, 37.0]	0.21
Gamma GT, UI/L		49 [18, 101]	30 [18, 56]	0.23
Alkaline phosphatase, UI/L		75.5 [65.5, 95.2]	72.5 [54.0, 87.5]	0.34
eGFR, ml/min		95.7 [49.3, 122]	101 [70.8, 122]	0.82
Urinary protein to creatinine ratio, mg/g		814 [453.6, 1916]	1738 [402, 2719]	0.31

Note: Continuous data are given as median [25th–75th percentiles].

resistance (MDR)-1 and glucocorticoid nuclear receptor subfamily 3, group C, member 1 (NR3C1). Variations in NR3C1 gene have been described and are associated with enhanced or reduced sensitivity to cortisol.[28–30] Some polymorphisms of the NR3C1 gene were associated with glucocorticoid response in paediatric patients with inflammatory bowel disease.[31] The MDR-1 gene encodes multidrug transporter P glycoprotein which functions as a transmembrane efflux pump; therefore it is important in the absorption, tissue targeting and elimination of different drugs. To date, more than 50 single nucleotide polymorphisms (SNPs) have been identified in the MDR-1 gene. Polymorphisms of MDR1 are associated with glucocorticoid response in patients with nephrotic syndrome.[32] However, the rarity of the SLE disease limits the investigation of this topic and no study investigating the role of MDR-1 and NR3C1 gene polymorphisms in the response to corticosteroids in lupus patients is currently available.

There is a general consensus that glucocorticoids have a wide therapeutic index and that there can be a significant delay between determining plasma dosage and the nuclear action in patients, which questions the use of therapeutic drug monitoring (TDM). Herein, we found that there is a dose-dependent effect on prednisolone bioavailability, which might decrease as prednisone doses increase. This means that increasing prednisone doses beyond a certain point may not improve the effective exposure to prednisolone, the active metabolite, potentially reducing therapeutic effectiveness. One of the other

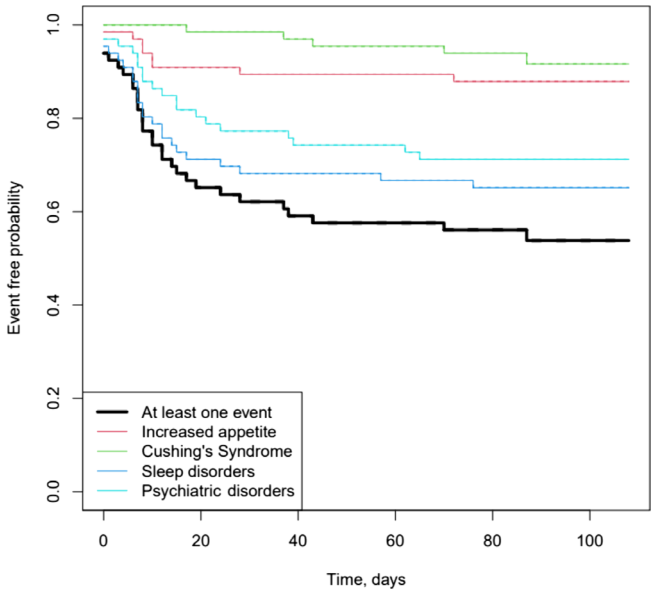

FIGURE 3 Kaplan-Meier representation for adverse event-free probability.

TABLE 4 Cox proportional-hazards regression models for adverse events data.

	Hazard ratio (95% CI)	*P*-value
At least one event		
Predinosolone $AUC_{0\text{-}24h}$	0.83 (0.55–1.27)	0.40
Predinosolone $fAUC_{0\text{-}24h}$	0.81 (0.53–1.23)	0.33
Increased appetite		
Predinosolone $AUC_{0\text{-}24h}$	0.87 (0.36–2.10)	0.76
Predinosolone $fAUC_{0\text{-}24h}$	0.88 (031–2.43)	0.79
Cushing's Syndrome		
Predinosolone $AUC_{0\text{-}24h}$	1.15 (0.11–12.1)	0.91
Predinosolone $fAUC_{0\text{-}24h}$	1.07 (0.16–7.15)	0.95
Sleep disorders		
Predinosolone $AUC_{0\text{-}24h}$	0.83 (0.54–1.27)	0.40
Predinosolone $fAUC_{0\text{-}24h}$	0.81 (0.52–1.26)	0.35
Psychiatric disorders		
Predinosolone $AUC_{0\text{-}24h}$	0.86 (0.48–1.55)	0.62
Predinosolone $fAUC_{0\text{-}24h}$	0.88 (0.48–1.60)	0.67

Note: $AUC_{0\text{-}24h}$ prednisolone area under the curve; $fAUC_{0\text{-}24h}$ predicted free prednisolone area under the curve.

main findings of the study is that cumulative exposure to prednisolone (AUC) was not significantly different between responders and non-responders after 3 months. This is in agreement with a previous study performed in a small cohort of SLE patients ($n = 8$) that failed to demonstrate a statistically significant link between drug exposure and disease activity.[3] These data support practical guidelines which advise limiting prednisone doses to a maximum of 30–60 mg/day for lupus patients and tapering off prednisone as soon as disease control is achieved.[33] This absence of association may be explained by the complex mechanism of action of glucocorticoids but also by several confounding factors that are difficult to control, such as intrinsic heterogeneity of SLE disease, different foundational drug treatments, or environmental and genetic factors. The limited range of the exposure metric (AUC) could also be another potential explanation. In the same way, no association between adverse effects and prednisolone exposure was observed in our cohort.

In the literature, pharmacokinetic targets are not clearly defined regarding either toxicity issues or efficacy and are warranted to make a valuable contribution to prednisolone TDM in the context of SLE.

We recognize certain limitations of this study. Its ability to identify more subtle relationships between prednisolone exposure and clinical outcomes might have been limited by the small size of the cohort, and the short follow-up of 3 months might have been insufficient to capture long-term outcomes, relapses or delayed adverse effects.

In conclusion, prednisolone cumulative exposure did not differ between responders and non-responders at Month 3 post-treatment in our cohort. These results do not support therapeutic drug monitoring to optimize steroid dosing in SLE.

AUTHOR CONTRIBUTIONS

NB, MS, GL and BBM contributed to the study conception and design. Material preparation and data collection were performed by LFB, LC, JMT, SB, JT, EH, PR, JH, AK, CRR, AJ, ZA, ED, AH, RS, JCL, SD, AB, DG, NCC, SF, IM, NJC and BBM. The first draft of the manuscript was written by NB and BBM and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors have no competing interests to declare in relation to this work.

DATA AVAILABILITY STATEMENT

Data from this study cannot be shared publicly as the procedures carried out with the French data privacy authority (CNIL, Commission nationale de l'informatique et des libertés) do not provide for the transmission of the database, nor do the information and consent documents signed by the patients. Consultation of the data by other interested researchers may be considered by AP-HP, subject to prior determination of the terms and conditions of such consultation and in respect of compliance with the applicable French and European regulations. The request must be addressed to the Delegation for Clinical Research and Innovation (DRCI) at secretariat-direction.drc@aphp.fr.

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REFERENCES

1. Tsokos GC. Systemic lupus erythematosus. *N Engl J Med*. 2011; 365(22):2110-2121. doi:10.1056/NEJMra1100359
2. Fangtham M, Petri M. 2013 update: Hopkins lupus cohort. *Curr Rheumatol Rep*. 2013;15(9):360. doi:10.1007/s11926-013-0360-0
3. Sagcal-Gironella ACP, Sherwin CMT, Tirona RG, Rieder MJ, Brunner HI, Vinks AA. Pharmacokinetics of prednisolone at steady state in young patients with systemic lupus erythematosus on prednisone therapy: an open-label, single-dose study. *Clin Ther*. 2011; 33(10):1524-1536. doi:10.1016/j.clinthera.2011.09.015
4. Potter JM, McWhinney BC, Sampson L, Hickman PE. Area-under-the-curve monitoring of prednisolone for dose optimization in a stable renal transplant population. *Ther Drug Monit*. 2004;26(4):408-414. doi:10.1097/00007691-200408000-00011
5. Gambertoglio JG, Vincenti F, Feduska NJ, Birnbaum J, Salvatierra O, Amend WJ. Prednisolone disposition in cushingoid and noncushingoid kidney transplant patients. *J Clin Endocrinol Metab*. 1980;51(3):561-565. doi:10.1210/jcem-51-3-561
6. Morton JM, Williamson S, Kear LM, McWhinney BC, Potter J, Glanville AR. Therapeutic drug monitoring of prednisolone after lung transplantation. *J Heart Lung Transplant*. 2006;25:557-563.
7. Abd Rahman AN, Tett SE, Abdul Gafor HA, McWhinney BC, Staatz CE. Exposure–effect relationship of mycophenolic acid and prednisolone in adult patients with lupus nephritis. *Br J Clin Pharmacol*. 2015;80:1064-1075.
8. Garg V, Jusko WJ. Bioavailability and reversible metabolism of prednisone and prednisolone in man. *Biopharm Drug Dispos*. 1994;15(2): 163-172. doi:10.1002/bdd.2510150208
9. Rollin C, Chosidow O, Diquet B, et al. Comparative study of availability of prednisolone after intestinal infusion of prednisolone metasulfobenzoate and prednisone. *Eur J Clin Pharmacol*. 1993;44(4):395-399. doi:10.1007/BF00316481
10. Jusko WJ, Rose JQ. Monitoring prednisone and prednisolone. *Ther Drug Monit*. 1980;2(2):169-176. doi:10.1097/00007691-198004000-00011
11. al-Habet SM, Rogers HJ. Urinary excretion of prednisolone following intravenous administration in humans. *J Clin Pharmacol*. 1989;29(10): 922-927. doi:10.1002/j.1552-4604.1989.tb03256.x
12. Frey FJ, Frey BM. Urinary 6 beta-hydroxyprednisolone excretion indicates enhanced prednisolone catabolism. *J Lab Clin Med*. 1983;101(4): 593-604.
13. Bright GM, Darmaun D. Corticosteroid-binding globulin modulates cortisol concentration responses to a given production rate. *J Clin Endocrinol Metab*. 1995;80(3):764-769.
14. Petersen KB, Jusko WJ, Rasmussen M, Schmiegelow K. Population pharmacokinetics of prednisolone in children with acute lymphoblastic leukemia. *Cancer Chemother Pharmacol*. 2003;51(6):465-473. doi: 10.1007/s00280-003-0602-3
15. Holford N, Heo Y-A, Anderson B. A pharmacokinetic standard for babies and adults. *J Pharm Sci*. 2013;102(9):2941-2952. doi:10.1002/jps.23574
16. Ceccarelli F, Perricone C, Massaro L, et al. Assessment of disease activity in systemic lupus erythematosus: lights and shadows. *Autoimmun Rev*. 2015;14(7):601-608. doi:10.1016/j.autrev.2015.02.008
17. Alexander SPH, Fabbro D, Kelly E, et al. The Concise Guide to PHARMACOLOGY 2019/20: Enzymes. *Br J Pharmacol*. 2019;176(S1):S297-S396.
18. Nugent CA, Eik-Nes K, Tyler FH. A comparative study of the metabolism of hydrocortisone and prednisolone. *J Clin Endocrinol Metab*. 1959;19:526-534.

19. El Dareer SM, Struck RF, White VM, Mellett LB, Hill DL. Distribution and metabolism of prednisone in mice, dogs, and monkeys. *Cancer Treat Rep*. 1977;61(7):1279-1289.
20. Hartiala J. Steroid metabolism in adult lung. *Agents Actions*. 1976;6(4):522-526. doi:10.1007/BF01973272
21. Baylis C, Brenner BM. Mechanism of the glucocorticoid-induced increase in glomerular filtration rate. *Am J Physiol*. 1978;234(2):F166-F170. doi:10.1152/ajprenal.1978.234.2.F166
22. de Truchis C, Bouazza N, Foissac F, et al. Prednisolone pharmacokinetics after oral prednisone administration in paediatric patients with kidney transplant. *Br J Clin Pharmacol*. 2023;89(5):1532-1540. doi:10.1111/bcp.15610
23. Mangin O, Zheng Y, Bouazza N, et al. Free prednisolone pharmacokinetics predicted from total concentrations in patients with inflammatory-immunonologic conditions. *Fundam Clin Pharmacol*. 2020;34(2):270-278. doi:10.1111/fcp.12515
24. Fernandez-Real J-M, Pugeat M, Grasa M, et al. Serum corticosteroid-binding globulin concentration and insulin resistance syndrome: a population study. *J Clin Endocrinol Metab*. 2002;87(10):4686-4690. doi:10.1210/jc.2001-011843
25. Bergrem HA, Bergrem H, Hartmann A, Hjelmesaeth J, Jenssen T. Role of prednisolone pharmacokinetics in postchallenge glycemia after renal transplantation. *Ther Drug Monit*. 2008;30(5):583-590. doi:10.1097/FTD.0b013e318187bb2f
26. Bergamaschi S, Rusconi R, Gervasoni M, Rigamonti AE, Cella S, Bareggi SR. Pharmacokinetics of prednisone and prednisolone in a case of hypothyroidism: effect of replacement therapy. *Steroids*. 2005;70:787-789.
27. Frey FJ, Horber FF, Frey BM. Altered metabolism and decreased efficacy of prednisolone and prednisone in patients with hyperthyroidism. *Clin Pharmacol Ther*. 1988;44(5):510-521. doi:10.1038/clpt.1988.188
28. Stahn C, Löwenberg M, Hommes DW, Buttgereit F. Molecular mechanisms of glucocorticoid action and selective glucocorticoid receptor agonists. *Mol Cell Endocrinol*. 2007;275(1-2):71-78. doi:10.1016/j.mce.2007.05.019
29. Mwinyi J, Wenger C, Eloranta JJ, Kullak-Ublick GA. Glucocorticoid receptor gene haplotype structure and steroid therapy outcome in IBD patients. *World J Gastroenterol*. 2010;16(31):3888-3896. doi:10.3748/wjg.v16.i31.3888
30. van Rossum EFC, Lamberts SWJ. Glucocorticoid resistance syndrome: a diagnostic and therapeutic approach. *Best Pract Res Clin Endocrinol Metab*. 2006;20(4):611-626. doi:10.1016/j.beem.2006.09.005
31. De Iudicibus S, Stocco G, Martelossi S, et al. Genetic predictors of glucocorticoid response in pediatric patients with inflammatory bowel diseases. *J Clin Gastroenterol*. 2011;45(1):e1-e7. doi:10.1097/MCG.0b013e3181e8ae93
32. Stachowski J, Zanker CB, Runowski D, et al. Resistance to therapy in primary nephrotic syndrome: effect of MDR1 gene activity. *Pol Merkur Lek Organ pol Tow Lek*. 2000;8:218-221.
33. Fanouriakis A, Kostopoulou M, Andersen J, et al. EULAR recommendations for the management of systemic lupus erythematosus: 2023 update. *Ann Rheum Dis*. 2024;83:15-29.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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