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Pharmacokinetic modeling of therapies for systemic lupus erythematosus

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Abstract

With the increasing use of different types of therapies in treating autoimmune diseases such as systemic lupus erythematosus (SLE), there is a need to utilize pharmacokinetic (PK) strategies to optimize the clinical outcome of these treatments. Various PK analysis approaches, including population PK modeling and physiologically based PK modeling, have been used to evaluate drug PK characteristics and population variability or to predict drug PK profiles in a mechanistic manner. This review outlines the PK modeling of major SLE therapies including immunosuppressants (methotrexate, azathioprine, mycophenolate and cyclophosphamide, among others) and immunomodulators (intravenous immunoglobulin). It summarizes the population PK modeling, physiologically based PK modeling and model-based individualized dosing strategies to improve the therapeutic outcomes in SLE patients.

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Keywords

azathioprine; cyclophosphamide; methotrexate; mycophenolate; pharmacokinetic modeling; systemic lupus erythematosus

Systemic lupus erythematosus (SLE) can affect both children and adults and is a systemic autoimmune disease characterized by the presence of autoantibodies. It is increasingly recognized that mechanisms leading to the clinical presentation with childhood-onset SLE (cSLE), which refers to SLE diagnosed prior to the age of 18 years, are multifactorial. As per current thinking, SLE results from a combination of genetic susceptibility, hormonal and environmental factors, including exposure to infections, drugs and sunlight. Dysregulation of both the innate and adaptive immune systems has been documented in patients with SLE. It includes abnormalities of toll-like receptors of the innate immune systems [1], abnormalities of T cells, B cells and antigen presenting cells of the adaptive immune systems, and more recently, abnormal activation and regulation of IFN-α [2]. Immunodysregulation results in the production of multiple antibodies against self-directed nuclear and cytoplasmic antigens. These antibodies can circulate in the body or form immune complexes that deposit in different organs leading to complement consumption and the production of inflammation cytokines, which leads to local inflammation and organ damage.

Although high-titer antinuclear antibodies are present in almost all children with cSLE, presence of antinuclear antibodies does not suffice for establishing a diagnosis of cSLE [3]. In general, cSLE affects girls more often than boys in a ratio of 8:1 and should be considered as a potential diagnosis in all patients who present with multi-organ system disease, with skin, joint and kidney involvement being most common.

Pharmacokinetics (PK) of drugs, which reflect drug concentration/exposure changes over the time course of therapy, could differ in various physiological or disease conditions [4]. Mechanic understanding of these changes is essential to determine how dosing regimens could be improved in SLE patients. The quantitative tools that support PK analysis include non-compartmental analysis (NCA), compartmental analysis and population PK analysis, and physiologically based PK (PBPK) modeling. Non-compartmental analysis [5] is a data-driven method which requires densely sampled PK data to calculate empirically integral measures including the area under the concentration-time curve (AUC), mean residence time, clearance (CL), volume of distribution (V_d), elimination rate constant (k_e) and terminal half-life ($T_{1/2}$)· The peak concentration (C_{max}) and time at which C_{max} is reached (T_{max}) could also be readily obtained·No prior knowledge about the above-mentioned PK parameters is needed to carry out non-compartmental analysis· Compartmental PK analysis [6] is also a data-driven method, which assumes the disposition of drugs according to compartments (one-compartment model, two-compartment model, three-compartment model, etc·) depending on the data fit by least squares or maximum likelihood procedures· Compartmental PK analysis could work with densely sampled data as well as sparsely sampled data, with the latter one usually requiring population PK modeling· Informed from the prior knowledge on PK parameters, population PK analysis estimates mean population level PK parameters as well as between-subject variability (innate to the study population)

and residual unexplained variability (e.g., assay variation) [7]. It also incorporates the effect of covariates such as patient demographics, clinical biomarkers, disease status, co-medications, and so on into the PK models to explain the variability in PK parameters. Since data from clinical studies are most likely to be heterogeneous and sparse in nature, it is common to utilize this population PK modeling approach to handle the clinical results. Once a population PK model is developed, stochastic simulation, based on the final population model and PK estimates, could be conducted to evaluate current dosing regimens against proposed therapeutic target or to adjust dosing regimens to improve the therapeutic target attainment in virtual patients, which is also called model-based Bayesian dose optimization [8,9]. PBPK modeling [10] is a predictive method utilizing multicompartment model to describe drug disposition in major tissues and organs based on physicochemical properties of drugs and physiological characteristics of body organs, prior to any experimental data obtained. It is used to predict PK profiles of a drug and to support its study design, and is then validated by the observed PK data obtained from a clinical study. The target-mediated disposition model can enable simulations of monoclonal antibody PK-pharmacodynamics profiles under various dosing regimens through investigating the relationships between monoclonal antibody, such as AMG 811, and its target, and identifying important contributions of baseline covariates to these relationships [11].

This review outlines the PK characteristics of these therapies for SLE and summarizes the population PK modeling and model-based individualized dosing strategies, in addition to outlining some of the PBPK modeling undertaken. There is now an amazing array of therapies used for the treatment of SLE, including immunosuppressants, immunomodulators, steroids and biologics. The latter two are not covered in this review due to page limits.

Methotrexate

Antifolate methotrexate (MTX) possesses excellent antiinflammatory and immunosuppressive activities. MTX is commonly indicated for the treatment of autoimmune diseases such as SLE [12–18]. Peak serum levels of this drug occur in 1–2 h. Its oral absorption appears to be dose-dependent with the mean bioavailability being around 60% at doses ≤30 mg/m^2 and much less absorption occurring at doses ≥80 mg/m^2, probably due to a saturation effect [19]. Consumption of food can delay absorption and significantly decrease peak concentration. Its peak serum concentration reaches after 30–60 min on intramuscular injection. MTX is readily available post intravenous administration; however, it is distributed in the peripheral tissues with initial volume of distribution being around 0.18 l/kg and steady-state volume of distribution around 0.4–0.8 l/kg. The PK disposition of MTX is best described by a two-compartment model. The transport of MTX across cell membranes involves the single-carrier-mediated active transport process. At serum concentrations ≥100 μmol, passive diffusion acts as a major pathway, leading to effective intracellular concentrations. In plasma, MTX is 50% protein-bound and may be displaced from albumin by various compounds including sulfonamides, salicylates, tetracyclines, chloramphenicol and phenytoin. The highest breast milk to plasma concentration ratio of MTX is 0.08:1. MTX is bioconverted into its polyglutamated metabolites through hepatic and intracellular metabolism. Polyglutamates can convert back to MTX by the action of hydrolase enzymes.

These active metabolites are inhibitors of dihydrofolate reductase and thymidylate synthetase. A part of MTX can be metabolized by intestinal flora post oral administration. The elimination of MTX is primarily through kidney, and dependent upon dosage and the route of administration. After intravenous administration, majority of MTX (around 80–90%) is excreted in the urine within 24 h. A finite amount (<10%) is excreted in the bile. The half-life ranges from 3 to 10 h at low doses (<30 mg/m^2) in patients receiving treatment for psoriasis or rheumatoid arthritis or low-dose antineoplastic therapy. CL rates of MTX generally decline at higher doses, and half-life ranges from 8 to 15 h at high doses. It has been identified that delayed drug CL is one of the major factors responsible for MTX toxicity. It has been postulated that the toxicity of MTX for normal tissues significantly relates to the duration of exposure to the drug rather than the peak level reached.

Due to the large variability in bioavailability of oral MTX and its urinary excretion, the response to MTX therapy and dose do not always correlate [20]. As the intracellular MTX polyglutamate levels drive the anti-inflammatory and immunomodulatory effects [12], it is highly recommended to measure the active metabolite MTX polyglutamate concentration in red blood cells (RBCs) to obtain a quantitative evaluation of MTX metabolism (Avise PG; Cypress Bioscience, Inc., San Diego, CA, USA). Previous studies have found that patients with MTX polyglutamate concentrations >60 nmol/1 after 3 months of MTX therapy were 5.5-fold more likely to have a clinical response than those with concentrations ≤60 nmol/1 (95% CI: 2.5–12.0) [20–22]. Patients with MTX polyglutamate concentrations <20 nmol/1 were 2.9-fold more likely to have an inadequate response than those with concentrations ≥20 nmol/1 (95% CI: 1.4–5.9) [20–22]. Through the MTX polyglutamate therapeutic drug monitoring, it could be determined whether non-responders or partial responders to MTX could benefit from switching from oral to parenteral administration, dose escalation or extended duration of MTX therapy.

In 2014, Poulin *et al.* reported a PBPK model of MTX that predicted distribution of MTX in subcutaneous xenografts of human tumor cell lines and healthy tissues in mouse. Briefly, the model took into account the partitioning of MTX into diverse fractions of the cells and interstitial space in tissues. The processes considered for predicting tissue-plasma partition coefficient (K_p) values under *in vivo* conditions are: nonspecific binding to neutral lipid equivalents, ionic binding to acidic phospholipids, binding to common plasma proteins such as albumin and/or lipoproteins, and drug ionization in the aqueous phase equivalent. The model resulted in reasonable prediction of K_p values in healthy tissues (muscle, lung, liver and brain) and human tumor xenografts (HCT-116, H2122 and PC3) in female nude mice for MTX. However, the model severely underestimated K_p value of liver for MTX, probably because of uptake by specific hepatic transporters (e.g., folate transporters) [23].

Azathioprine

Azathioprine (AZA), a prodrug of 6-mercaptopurine (6-MP), is used for the management of SLE, in combination with corticosteroids. AZA is almost completely converted to 6-MP, which is mediated by glutathione and similar compounds in the intestinal wall, liver and RBCs, without the aid of enzymes. The nucleoprotein metabolites of 6-MP may be

associated with suppression of DNA synthesis by inhibiting the enzymatic conversion of inosinic acid to xanthylic acid and adenylosuccinic acid to adenylic acid [24].

AZA is highly lipophilic and can be well absorbed (about 80%) after oral administration. Its oral bioavailability varies from 30 to 90% among individual patients due to partial inactivation in the liver. The peak serum levels of the drug and its active metabolite 6-MP are reached in 1–2 h. AZA and 6-MP are approximately 30% bound to plasma proteins while circulating in the blood stream [25]. Van and colleagues performed a detailed study of 6-MP and AZA PK after intravenous and oral AZA administration in healthy adults [26]. The blood concentration values after intravenous administration of AZA were fit to a two-compartment model. The median (range) CL and volume of distribution at steady state (V_{dss}) of 6-MP after intravenous AZA administration were 3.3 1/kg/h (2.4–6.7) and 5.6 l/kg (3.9–15.5), respectively [26]. AZA can be extensively metabolized and cleaved to 6-MP, which is metabolized analogously to natural purines. The end products of AZA metabolism are 6-thiouric acid (38%) and various methylated and hydroxylated purines, which are excreted via the urine. They are rapidly eliminated from blood. The average plasma half-life is 26–80 min for AZA itself and 3–5 h for AZA plus its metabolite 6-MP. No AZA or 6-MP is detectable in urine after 8 h.

Thiopurine methyltransferase (TPMT) is the major metabolic route for inactivation of thiopurine drugs in the bone marrow. When TPMT activity is low, it is predicted that proportionately more 6-MP is converted into thioguanine nucleotide (6-TGN, the active metabolite), which accumulates in the bone marrow and causes excessive toxicity under standard doses of AZA or 6-MP. In order to prevent potentially life-threatening adverse drug reactions, the US FDA recommends that TPMT activity be evaluated before initiating immunosuppressant therapy with AZA or 6-MP [27]. Aside from TPMT genotype test, the TPMT RBC assay is a preferred test to identify individuals with low TPMT activity who may be at risk for excessive myelosuppression [28]. The activity of TPMT is measured by the amount of 6-methylmercaptopurine nucleotide (the inactive metabolite) per 1 ml of packed RBCs (U/ml) with the normal range between 25 and 65 U/ml. Individuals with low TPMT activity (<25 U/ml) are at high risk of bone marrow toxicity and a dose reduction and therapeutic drug monitoring are recommended [28]. Patients with high TPMT activity (>65 U/ml) are at risk for therapeutic failure and may require higher than the standard doses and therapeutic drug monitoring [28].

Thiopurine metabolite test is another surrogate test of TPMT activity to optimize the dosing regimens of AZA or 6-MP. 6-TGN may increase the risk of leukopenia at high blood concentrations or cause inadequate clinical response when its concentration falls. 6-Methylmercaptopurine nucleotide may cause hepatotoxicity at high blood concentrations. The normal reference range is 230–400 pmol/8 × 10^8 RBCs for 6-TGN in inflammatory bowel disease or <5700 pmol/8 × 10^8 RBCs for 6-methylmercaptopurine nucleotide [29,30]. Askanase *et al.* showed that clinical responses in SLE can occur at levels of 6-TGN lower than the target range established for inflammatory bowel disease [31].

Mizoribine

Mizoribine (MZR), an imidazole nucleoside, is a novel immunosuppressive agent used to prevent rejection post renal transplantation, lupus nephritis, rheumatoid arthritis and nephrotic syndrome [32]. The immunosuppressive effect of MZR is attributed mainly to its inhibition of the proliferation of lymphocytes by blockade of nucleic acid synthesis [33]. The clinical efficacy of MZR for the treatment of autoimmune disease, especially in conditions like lupus nephritis, was investigated in various institutions and its clinical usefulness was prominent. Moreover, MZR is well tolerated with very less adverse events and has similar effect as mycophenolate mofetil (MMF) in the induction therapy of active lupus nephritis at a dose of 300 mg every other day after oral administration [34]. Stypinski *et al.* evaluated the PK data of higher-dose MZR via oral administration, in which 24 healthy Caucasian males participated in a single-dose (3, 6, 9, 12 mg/kg/day) study and 12 subjects participated in a multi-dose (6, 12 mg/kg/day) study [35]. The single-dose exposure (C_{max} and AUC) of MRZ increased relatively proportionately with dose within the 3–12 mg/kg dose range. The median T_{max} of MRZ ranged from 2 to 2.5 h for all single-dose levels; mean half-life stayed at slightly below 3 h; oral CL (CL/F) remained at approximately 0.19 l/h/kg; and apparent volume of distribution following oral administration (V_d/F) was at 0.78 1/kg. In the multiple-dose study, MZR reached peak concentrations (C_{max}) within 2–3 h, followed by an elimination phase with a median 3 h half-life. MZR reached peak concentrations within 2–3 h and was eliminated mostly via the kidney (>65% of dose) with 3 h elimination half-life [35]. This PK study demonstrated that 12 mg/kg/day dose level is required to maintain steady-state concentration within the therapeutic window between 0.5 and 3.0 mg/ml in subjects with normal renal function. Based on the above PK data, another group estimated the population PK parameters of MRZ using a non-linear mixed effects model program [36]. PK parameters of MZR in 36 individual subjects were obtained from population estimates according to Bayes' theorem using the non-linear mixed effects model *post-hoc* option. The mean values of the absorption lag time, absorption rate constant (K_a) and apparent distribution volume (V/F) were estimated to be 0.349 h, 0.869 h^{-1} and 0.834 l/kg, respectively. Oral CL (CL/F) was modeled with creatinine clearance (CrCL), and the mean value was estimated to be 1.93 l/h. These parameters indicated that orally administrated MZR is rapidly absorbed from the gastrointestinal tract, distributed into the tissue, and excreted predominantly in urine via glomerular filtration and tubular secretion. In addition, K_a, V/F and CL/F in the single-dose study were almost constant at a dose range of 3–12 mg/kg and were similar to those in the multiple-dose study. The PK of MRZ is well described by a simple one-compartment model with first-order absorption.

As the elimination rate of MZR is highly dependent on renal function, the PK studies of the patients with SLE and/or lupus nephritis have been under great concern. MZR was not very effective in children with moderate-to-severe SLE [37]. To evaluate the efficacy of MZR in children with SLE, Nozu *et al.* administered oral MZR at a high dose (300 mg/day) to five adolescents with SLE [38]. The C_{max} of MZR was 1.33 μg/ml or higher in all five patients. The efficacy and safety of high-dose MZR therapy were satisfactory, which may warrant its application to steroid-dependent pediatric patients with SLE. In another study, an adolescent girl with lupus nephritis was given two different total daily dosages of MZR (250 and 300

mg). The maximum serum levels were obtained within 2 h. Estimated values for AUC and half-life were 3.33 μg·h/ml and 1.87 h for a daily dosage of 250 mg, and 3.80–8.80 μg·h/ml and from 1.51 to 4.19 h for a daily dosage of 250 mg, respectively.

Fludarabine

Fludarabine is administered by intravenous and oral routes as a phosphate prodrug [39]. Fludarabine is effectually trapped in blood due to its ionization at physiological pH, leading to some level of specificity for blood cells. Its active metabolite, fluoro-arabinofuranosyladenine (F-ara-A), targets lymphocytes and inhibits DNA synthesis by interfering with ribonucleotide reductase and DNA polymerase [40,41]. Its oral bioavailability ranges from 50 to 65%. T_{max} is 1–2 h and can be delayed to the range of 1.3–2.2 h by a high-fat meal. Plasma protein binding of fludarabine ranges from 19 to 29%. Fludarabine is rapidly dephosphorylated to F-ara-A and then phosphorylated by deoxycytidine kinase to F-ara-A triphosphate. Fludarabine undergoes extensive metabolism and rapidly disappears from plasma with a tri-exponential decay. The terminal half-life of F-ara-A is around 20 h. Plasma CL is 117–145 ml/min by intravenous administration. Renal CL represents approximately 40% of the total body CL. Kuo *et al.* reported that subcutaneous and intravenous administration of fludarabine appears to have similar PK in patients with lupus nephritis [42]. A linear two-compartment model can best describe the PK of F-ara-A. Bioavailability of F-ara-A after subcutaneous dosing was approximately 5% higher than the bioavailability after intravenous administration. F-ara-A demonstrated a median distribution half-life of 57 (interquartile range 56–66) min and a terminal elimination half-life of 10.3 (8.5–10.4) h. T_{max} after subcutaneous administration was 2 (1–2) h. Median C_{max} was 0.51 (0.38–0.56) and 0.75 (0.52–0.91) mg/l after subcutaneous and intravenous administration, respectively. No significant differences in AUC, renal CL, excretion rate or percentage of dose excreted in urine were detected between subcutaneous and intravenous administration. Its CL is influenced by renal function.

Mycophenolic acid

Mycophenolic acid (MPA) is a potent immunosuppressant that inhibits the *de novo* synthesis pathway of guanosine nucleotides, which triggers a potent cytostatic effect on T and B lymphocytes, thereby inhibiting proliferative response [43]. MMF is the ester prodrug of MPA that is administered orally and is widely used in the treatment of SLE [44]. On oral administration, MMF is rapidly absorbed and hydrolyzed by esterases to its active metabolite MPA, which is largely metabolized to the inactive metabolite MPAG (7-O-MPA glucuronide). MPA shows high plasma albumin binding (>90%); however, MPAG can displace MPA from its albumin-binding site and increase its free fraction. Biliary-excreted MPAG can be hydrolyzed back to MPA during enterohepatic circulation (EHC) and reabsorbed as MPA, which is attributable to the total MPA exposure of approximately 40%, with a range of 10–60% [45]. To date, various approaches have been explored for the PK studies of MPA and MPAG. In this review, 17 published papers regarding PK modeling of MMF for patients with SLE were selected and reviewed. The specific details of each study are presented in TABLE 1. In the study undertaken by Jiao *et al.* which involved healthy subjects, 5 studies used data collected from pediatric patients with SLE and 11 published

papers included PK studies from adult patients. Some studies established an EHC model that combines MPA and MPAG simultaneously based on physiological aspects or biliary excretion [43,46–48]. A constant represents the rate of filling the gallbladder from the central compartment. Emptying of the gallbladder into the gastrointestinal compartment is dependent on two time points with rate and duration. Sherwin *et al.* developed a six-compartment model including a gallbladder compartment with first-order absorption and a single series of transit compartments in pediatric and adolescent patients with cSLE [48]. Compared with conventional empirical models, this population PK model incorporates physiological aspects associated with MPA disposition successfully, contributing to optimally individualized drug therapy. de Winter *et al.* established a two-compartment model with first-order elimination [46]. The absorption of MPA with a double-peak model was described under two first-order processes with a short and a long lag time through the short and long absorption compartments and subsequent first-order elimination. A five-compartment model provided by Jiao *et al.* characterized an EHC model including both MPA and MPAG simultaneously in healthy Chinese subjects [47]. The researchers reported that the model had no effect on the PK of MPA and MPAG.

Zahr *et al.* used one-compartment model with first-order elimination and triple γ distribution to describe the PK profile of MPA in patients with SLE [49]. The triple γ distribution offers a best fit to the third peak in addition to the first and second absorption peaks in adult patients with SLE; hence, it can provide a good Bayesian estimator. The later peak or third peak is contributed by the re-conversion to MPA from MPAG during EHC in the SLE study. Another study undertaken by Woillard *et al.* pooled data from pediatric patients with cSLE and developed one-compartment model with first-order elimination and absorption [50]. An iterative two-stage Bayesian approach was successfully applied to develop PK model and a Bayesian estimator, which allowed good AUC estimation performance. Most of the studies used non-compartment model to predict the PK parameters of MMF in SLE patients with various software such as WinNonlin, In-house software, Analyse-it, GraphPad, SAS, R, etc. [51–62].

SLE activity is strongly correlated with MPA $AUC_{0–12}$ in SLE patients receiving a stable MMF dose [63]. As Zahr *et al.* reported, MPA $AUC_{0–12}$ was weakly correlated with MMF dose ($r = 0.33$, $p = 0.005$) [63]. MPA $AUC_{0–12}$ in active SLE patients group was significantly lower than that in inactive SLE patients group (Mean ± standard deviation 26.8 ± 13.6 vs 46.5 ± 16.3 μg-h/ml; $p < 0.0001$). MPA $AUC_{0–12}$ was negatively correlated with the SLE Disease Activity Index ($r = −0.64$, $p < 0.0001$) [63]. In multivariate analysis, MPA $AUC_{0–12}$ was the sole parameter associated with SLE activity (odds ratio 0.89 [95% CI: 0.83–0.96]; $p = 0.002$). The MPA $AUC_{0–12}$ threshold value of 35 μg·h/ml was associated with the lowest risk of active SLE [63]. An individualized dosing regimen of MMF, with a target $AUC_{0–12}$ of 35 μg h/ml, should be achieved for SLE patients.

A physiologically realistic model to better describe the PK of MPA and MPAG was reported by Wai-ping *et al.* in 2009. This report particularly focused on quantitative description of the EHC of MPA and MPAG, and also characterized and assessed the impact of cyclosporine A (CsA) dose on the extent of EHC of MPA and MPAG after oral administration of MMF in Asian renal transplant recipients. The plasma concentration-time data of MPA and MPAG

were fitted to a five-compartment drug and metabolite EHC model, which incorporates a physiologically realistic time-varying gallbladder emptying process. The application of the model facilitated the estimation of PK parameters of both MPA and MPAG in 14 renal transplant patients after oral administration of MMF. The model also provided greater insight into EHC process and its influence on the disposition kinetics of MPA and MPAG in patients with or without CsA administration. Increase in CsA dose decreased the extent of EHC for both MPA and MPAG, suggesting a dose-dependent impact on CsA-mediated inhibition of MPAG biliary excretion [64].

In 2013, Malmborg *et al.* reported a PBPK model linked to an *in vitro/in silico in vivo* extrapolation (IVIVE) approach after oral administration of MMF [65]. The PBPK model was developed according to the lumping principle and was a six-compartment model representing the following: the lung; heart, brain and kidney; gut, stomach, spleen and pancreas; the liver; muscle, bone, skin and testes; and adipose tissue. The IVIVE method included prediction of human absorption rate constant from caco-2 permeability data, measurement of prodrug conversion rate constant in human intestinal fluid, prediction of human hepatic CL from human hepatocytes, measurement of the extent of prodrug conversion in human liver S9 fraction, measurement of the prodrug conversion rate in human blood and measurement of plasma protein binding. The PBPK-IVIVE model adequately predicted the high bioavailability of MPA when given orally as MMF. The reported model also adequately described that rapid conversion and absorption of MMF resulted in an early MPA T_{max}, which is also influenced by the fast absorption and the high CL of MPA itself. However, the observed PK profile of MMF with a rapid decay phase followed by a much slower terminal elimination phase was not captured by the model [65].

Cyclophosphamide

Cyclophosphamide (CYC) is an alkylating and immunosuppressive agent successfully used for the treatment of SLE, vasculitis and other autoimmune diseases [66–68]. CYC is a prodrug that is converted in the liver to its active alkylating metabolite, phosphoramide mustard, which binds to DNA and reacts with purine bases to form double-stranded adducts [67,69]. It can be administered either orally or intravenously [70–72]. Plasma PK of CYC was described by a two-compartment model. CYC is well absorbed orally with a bioavailability greater than 75% [73]. Maximum plasma concentrations of metabolites were reached at 2–3 h after an intravenous dose [74]. CYC is rapidly distributed throughout the body. It has low plasma protein binding (around 20%), but its metabolites are bound to an extent greater than 60%. CYC is eliminated primarily in the form of metabolites, but 5–25% of the dose is excreted in urine as unchanged drug. The half-life of CYC is between 3 and 12 h. Metabolites may be elevated, but no increased clinical toxicity was observed in patients with renal function impairment. However, dosage adjustment may be necessary for patients with severe renal impairment [75,76].

Cyclosporin A

CsA, a calcineurin inhibitor with potent immunosuppressive activity, has been used in trials in the treatment of patients with SLE [77,78]. Oral CsA has been suggested to be an efficient

and safe treatment alternative to intravenous pulse CYC to induce durable remission in the treatment of proliferative lupus nephritis and lupus membranous nephropathy [78–82]. Because of its unique selectiveness and less-severe side effects, CsA is increasingly used in autoimmune diseases [83] and served as a second-line induction therapy in patients with active lupus nephritis unresponsive to conventional therapy [84]. The main concern about the use of CsA in lupus nephritis is nephrotoxicity, which is usually dose related [85,86]. In 1981, CsA was firstly given to five patients with active SLE at a dose of 10 mg/kg/day orally [87]. It was not possible for any patient to take the drug for longer than 7 weeks because of side effects including nephrotoxicity. In SLE, good results were obtained with reduced doses of CsA ranging between 3 and 5 mg/kg/day and proportional reduction of side effects [83,88–91].

CsA absorption from the gastrointestinal tract is incomplete and varies widely both within and between patients, leading to wide bioavailability range of 5–80% [86,92,93]. Absorption is significantly affected by solubilization of CsA in bile, diet, gastrointestinal transit time and concurrent medications. Peak concentration of CsA is reached in 1–8 h after oral administration. Different models such as two-compartment PK model with first-order absorption and a one-compartment open model with first-order absorption and elimination have been developed for the PK of CsA. Measurement of the drug concentration in the whole blood is rarely required in autoimmune diseases, except in case of doses greater than 3 mg/kg/day. Clinical response to CsA is relatively slow and occurs within 1–2 months after treatment. CsA is metabolized to more than 20 metabolites and excreted mainly in the bile. Although its elimination is not altered in renal insufficiency, CsA should be avoided in patients with impaired renal function due to its nephrotoxic effects. Bioavailability of CsA solution is similar to capsule formulations. CsA Sandimmune® has a poor bioavailability and large inter-and intra-patient PK variability [92]. Neoral® is a new microemulsion formulation of CsA. It has greater and more balanced gastrointestinal absorption, improved bioavailability and smaller inter-patient variability in PK profiles than conventional oil-based formulations, indicating more consistent and more predictable absorption of CsA from microemulsion formulations [94,95]. Higher C_{max} and AUC were achieved during the steady state in patients who received Neoral. PK study of CsA was also performed with a single 5 mg/kg dose of either CsA capsules or Neoral administered orally to 10 pediatric patients with lupus nephritis [79,96]. Neoral had a higher C_{max} (943 ± 176 vs 697 ± 187 ng/ml) and AUC (4612 ± 785 vs 3483 ± 873 ng·h/ml) compared with CsA capsules. There was no difference in T_{max} and half-life between the two groups. Furthermore, Neoral showed a significant increase in growth rate over the prednisolone plus CYC group, and also showed improvement of growth status [79].

Intravenous immunoglobulin

Intravenous immunoglobulin (IVIG) is derived from the plasma of a large pool of healthy donors by cold ethanol fractionation [97]. It typically contains more than 90% unmodified IgG and only trace amounts of IgA or IgM [98]. It shows different immunomodulating activities and has been used successfully to treat clinical manifestations of SLE, including refractory thrombocytopenia, pancytopenia, central nervous system involvement, secondary antiphospholipid syndrome and nephritis [99–101]. Since to date, FDA has only approved

few drugs such as hydroxychloroquine, corticosteroids, belimumab and aspirin in treating SLE, the use of IVIG in SLE patients remains off-label and unlicensed. As such, patients with lupus nephritis are recommended to receive IVIG under close monitoring and after adequate hydration to correct volume depletion [102]. The IVIG preparation brands marked in the USA include Gammagard S/D®, Gammar-IV®, Gamimune-N®, Iveegam®, Polygam S/D®, Sandoglobulin®, Venoglobulin-I® or Venoglobulin-S®, Carimune/Panglobulin®, Hizentra®, Octagam®, Privigen® and Gamunex®.

Serum IgG concentration immediately increases after IVIG infusion, then falls following a biphasic plasma elimination curve with an initial rapid decline in the first week and a slower decay thereafter. The initial rapid decline is attributable to passage of IgG out of the vasculature into lymph and extracellular fluid compartment; the subsequent decay is mainly because of catabolism when IgG in lymph and tissues slowly distributes back into the circulation. As two-compartment model is mostly used for IgG concentration in healthy individuals, IgG concentration decay curve may be subdivided into early phase (α) and late phase (β). However, some studies use alternative pharmacologic models such as non-compartment and single compartment [103]. To date, most studies derive an empiric serum or plasma decay half-life as the principal PK parameter of the infused IgG. PK parameters of IVIG have been evaluated in a randomized, double-blind, parallel-group study of 30 healthy subjects with normal serum IgG levels [104]. Commercial Sandoglobulin (IVIG) was compared with two test formulations such as Sandoglobulin-Nanofiltered (IVIG-N) and Sandoglobulin-Liquid (IVIG-L). PK parameters were derived by a modelindependent method. Product equivalence was demonstrated for IgG C_{max} and AUC to the last sampling time point $AUC_{(0\text{-}tz)}$ for three test formulations. Peak serum concentrations of IgG by the contribution of IVIG were 7.9 ± 1.4 g/l for IVIG, 8.3 ± 1.6 g/l for IVIG-N and 8.6 ± 0.8 g/l for IVIG-L. Corresponding AUCs were between 126 and 128 g · day/l for all three formulations. CL, calculated as dose/AUC, was 0.30–0.32 l/day. Likewise, there was no statistical significant difference ($p > 0.05$) between product half-lives: 28 ± 9 days for IVIG, 30 ± 13 days for IVIG-N and 24 ± 9 days for IVIG-L.

A two-center study on PK of IVIG was reported before and during pregnancy in healthy women with poor obstetrical histories [105]. Weight-adjusted dosage of IVIG was between 0.5 and 1.0 g/kg. Sampling was performed pre-pregnancy and in the first and second trimesters. Estimated AUCs by the contribution of IVIG were non-significant: 4890.8 g · h/l for prepregnancy, 5591.4 g · h/l for the first trimester and 4755.1 g · h/l for the second trimester. The overall estimated contribution of IVIG was approximately 4000 and 6400 g · h/l for the IVIG 0.5 and 1.0 g/kg subgroups, respectively.

Neonates have low levels of IgG at birth, and IVIG has provoked interest in its potential use in preventing or treating infections in neonates [106–112]. PK and safety of IVIG in very low birth weight (VLBW) infants have been frequently studied. Twenty VLBW neonates with birth weights from 750 to 1500 g were randomly assigned to receive a single dose of IVIG 0.5 or 0.75 g/kg during the first week of life [109]. Mean peak IgG concentrations were 1.564 and 1.316 g/dl for the high-dose and lowdose groups, respectively. Mean IgG concentrations were very similar for both groups during 28 days. Similar to the PK profile in adults, serum IgG concentrations at least doubled after IVIG infusion, then decreased

rapidly, following which it showed a more gradual decrease. The terminal elimination rate constant was between 0.023 and 0.058 day^{-1}. Mean elimination half-lives were similar and around 23 days. In another study by the same group of authors, similar PK results were obtained in 21 VLBW neonates receiving IVIG 0.5, 0.75 or 1.0 g/kg as a single dose. In another study by the same group of authors, 21 VLBW neonates received IVIG 0.5, 0.75 or 1.0 g/kg as a single dose and showed similar PK results [110]. IVIG concentrations did not correlate with birth weight by linear regression analysis. Peak concentration was reached 15 min after infusion. The mean peak concentrations were proportional to the dose and were 1.826, 1.476 and 1.257 g/dl for the large-, intermediate-and small-dose groups, respectively. The terminal elimination rate constant was 0.024–0.035 day^{-1} in each group. The CL was between 3.7 and 5.6 ml/kg/day. The volume of distribution was between 0.13 and 0.26 l/kg. The half-life was between 20 and 29 days. The wide variability observed indicates the necessity of individualization of IVIG in VLBW neonates. Other studies investigated IVIG 0.5–1.3 g/kg in high-risk infants [111,112]. Volume of distribution had no correlation with birth weight. The volume of distribution was between 0.08 and 1.1 l/kg. The CL was 2.0–2.8 ml/kg/day. The elimination half-life was 16–32 days.

Five-year view

Suboptimal therapy with immunosuppressive or immunomodulating agents in patients with SLE remains an important clinical concern due to its potential long-term adverse consequences. Personalized treatment and precision dosing are challenging due to large, unexplained variability in drug exposure (PK) and response (pharmacodynamics) that arises from pharmacogenetic/genomic and environmental factors. There are few clinical factors that reliably predict this variability in drug disposition and effects, and current dosing in patients with SLE is largely by ‘trial and error’. PK modeling has allowed the quantitative description of the PK (and sometimes the pharmacodynamics) of immunosuppressive or immunomodulating agents with identification of important predictive clinical factors of between-patient variability (covariates). The next step will be implementation of these models into clinical software to enable adaptive feedback using sparse concentration measurements and biomarker response [8]. Envisioned systems will be comprehensive decision support tools for tailoring dose to individual needs that will maximize the probability of therapeutic efficacy while minimizing the adverse events [49,50,113–115].

Expert commentary

The steady increase in the use of immunosuppressive/immunomodulating medications for SLE treatment necessitates the need to optimize the therapeutic outcomes through PK strategies. Large between-and within-subject PK variability has been reported with these therapies. As there is a strong relationship between the drug exposure and therapeutic effect, the relationship between drug dose and exposure (AUC) still remains to be fully defined due to the large PK variability. Population PK modeling, PBPK modeling and model-based individualized dosing strategies have been proposed over the past 10 years to evaluate the PK characteristics by incorporating patient-specific factors. These models have evolved from the empirical compartmental modeling to more complex mechanism-based iterations, with

more recent use of PBPK to explain PK variability with physiological plausibility, such as enterohepatic recycling and pharmacogenetic polymorphisms.

In recent years, there has been greater exploration of the biological factors that impact the PK of therapies used in autoimmune diseases. This includes major advances in understanding the drug transporters, metabolizing enzymes, drug-drug interactions, pharmacogenetic polymorphisms and the roles they play in PK variability. It is of critical importance to determine whether these factors, which may contribute significantly to PK variability, can be utilized in the development of population PK models and if these can be utilized clinically. Patient factors, such as impaired renal or hepatic function and genetic polymorphisms in drug metabolizing enzymes and transporters, are associated with PK variability of immunosuppressants and need to be more closely considered when developing PK strategies to optimize the therapeutic outcomes. All the components that influence drug exposure, such as biotransformation, drug transport, bile physiology and gut flora, can be included to build population PK models or PBPK models. Some PK models developed to date show promise in describing the impact of physiological processes or pharmacogenetic polymorphisms; however, others just provide confirmatory information of already known PK.

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Key issues

- There are now an amazing array of therapies used for the treatment of systemic lupus erythematosus, including immunosuppressants (methotrexate, azathioprine, mycophenolate and cyclophosphamide, among others) and immunomodulators (intravenous immunoglobulin).
- Many of these drugs exhibit large between-variability in pharmacokinetics (PK), resulting in a wide range of exposure (and response) at standard dose.
- Population modeling approaches allow to quantitatively describe PK behavior and variability in patients and identify the factors that influence changes in the relationship between the administered dose and the achieved concentrations.
- These population models can be implemented in Bayesian estimators to facilitate real-time dose adjustment to defined target concentrations using concentration and biomarker measurements as feedback.
- An attractive approach uses population models as prior information, from this we can estimate each patient's PK parameter values to construct a patient-specific Bayesian posterior model based on that patient's relevant demographic characteristics, dosage history, and drug and biomarker concentrations.
- These individualized and tailored dosing approaches guided by PK algorithms may be safer, more effective and even cost-effective.

Table 1

pharmacokinetic models for mycophenolic acid.

patients	Disease	Dose	Outline of PK model	Software	PK parameter estimates	Model variability	Covariates	Model assessment	Concomitant medication	Ref.
dren (12 ± 3	Autoimmune including 10 SLE patients	Mean starting dose 974 ± 282 mg/m^2 per day; mean following dose 441 ± 140 mg/m^2	Non-compartmental model	GraphPad	MPA $AUC_{0–12\ h}$ 61.8 ± 31.0 μg·h/ml; mean T_{max} 60 min; mean C_{max} 18.5 ± 8.4 μg·ml; mean apparent CL 2.21 ± 1.14 ml/min; MPAG $AUC_{0–12\ h}$ 680.7 ± 597.0 μg·h/ml	NS	NS	NS	Prior to the start of MMF: prednisone, IVIG, azathioprine, cyclosporine	[51]
	Healthy male	0.5 g	Five compartments including GI compartment, MPA central compartment, MPAG central compartment, gallbladder compartment and peripheral compartment	NONMEM	T_{lag} (h) 0.0956 [15.8]; K_{12} (h^{-1}) 3.53 [12.4]; Q/F (l/h) 16.1 [5.10]; MPA CL/F (l/h) 10.2 [5.70]; MPGA CL/F (l/h) 1.38 [6.90]; V_2/F (l) 12.5 [8.30]; V_3/F (l) 213 [9.10]; V_4/F (l) 4.40 [6.40]; K_{51} (h^{-1}) 67.5 [12.7]	BSV (%): T_{lag} (%) 57.3 [44.5]; K_{12} (%) 60.3 [31.9]; Q/F (%) 13.7 [48.9]; MPA CL/F (%) 18.9 [35.6]; V_2/F (%) 34.5 [48.7]; V_3/F (%) 22.7 [39.2]; V_4/F (%) 23.1 [37.3]; EHCP (%) 1.33 [27.2]; θ (%) 1.33 [27.2] ; RUV:PropMPA (%) 45.3 [9.3]; PropMPAG (%) 20.8 [16]	Body weight on CL/F of MPA and MPAG, and V_3	Diagnostic plots, crossmethod validation, visual predictive check	NS	[47]
	Autoimmune including 12 SLE patients	1 g	Non-compartmental model	WinNonlin	T_{max} (h) 0.94 [0.44]; C_{max} (mg/l) 20.2 [10.9]; $AUC_{0–12\ h}$ (h·mg/l) 66.0 [22.0]; $AUC_{0–24\ h}$ (h·mg/l) 97.0 [34.5]; $C_{12\ h}$ (mg/l) 3.6 [2.7]; $C_{24\ h}$ (mg/l) 2.4 [2.1]	BSV: T_{max} (%) 46.8; C_{max} (%) 53.8; $AUC_{0–12\ h}$ (%) 33.3; $AUC_{0–24\ h}$ (%) 35.6; $C_{12\ h}$ (%) 74.2; $C_{24\ h}$ (%) 85.8	NS	Diagnostic plots	Prednisolone	[52]
	6 Lupus nephritis versus 24 kidney transplantations	2 g/day	Non-compartmental model	WinNonlin, SPSS	MPA: $AUC_{0–12\ h}$ (μg·h/ml) 41.0 (15.3–62.5); C_0 (μg/ml) 2.25 (0.37–4.58); C_{max} (μg/ml) 5.03 (2.29–8.85); CL/F (ml/min) 301 (148–804) MPAG: $AUC_{0–12\ h}$ (μg·h/ml) 646 (98.4–1032); C_0 (μg/ml) 40.9 (1.21–87.0); C_{max} (μg/ml) 82.8 (22.3–110)	NS	NS	NS	Prednisolone	[53]

patients	Disease	Dose	Outline of PK model	Software	PK parameter estimates	Model variability	Covariates	Model assessment	Concomitant medication	Ref.
					Dose-normalized MPA $AUC_{0–12\ h}$ (μg·h/ml per mg/kg) 2.19 (0.87–4.23); C_0 (μg/ml per mg/kg) 0.11 (0.03–0.31); C_{max} (μg/ml) 0.36 (0.13–0.45) Dose-normalized MPAG $AUC_{0–12}$ (μg·h/ml per mg/kg) 35.0 (8.34–69.8); C_0 (μg/ml per mg/kg) 2.18 (0.10–5.89); C_{max}(μg/ml) 4.46 (1.89–6.26) MPA CL/F (ml/min/kg) 5.64 (2.91–14.2) MPAG $AUC_{0–12\ h}$/MPA $AUC_{0–12\ h}$ 9.76 (3.62–39.1); MPAG C_0/MPA C_0 10.7 (2.08–33.5); MPAG $AUC_{5–12\ h}$/$AUC_{0–12\ h}$ 0.44 (0.35–0.56)					
	SLE	0.5–1.5 g	One-compartment model with first-order elimination convoluted with a triple γ distribution	In-house software	T_{max} (h) 1.1 [1.2]; V_d/F (l) 32.7 [18.6]; CL/F (l/h) 40.3 [50.7]	NS	NS	Diagnostic plots, jack-knife method	Prednisolone	[49]
	Autoimmune with 12 SLE patients	1 g	Two-compartment model with first-order absorption and first-order elimination	NONMEN	F_{fast} 0.71 [9]; $T_{lag,\ short}$ (h) 0.287 [5]; $T_{lag,\ long}$ (h) 0.645 [3]; K_a (h^{-1}) 6.2 [22]; V_c (l) 52.4 [17]; CL (l/h) 8.27 [5]; V_p (l) 262 [5]; Q (l/h) 16.2 [22]; T_{GB1} (h) 6; D_{GB} (h) 0.1; EHCP 0.37; K_{63} (h^{-1}) 1	BSV: $T_{lag,\ short}$ (%) 32; K_a (%) 182 [40]; CL (%) 34 [41]; V_c (%) 53 [48]; T_{GB1} (%) 200; EHCP (%) 35; RUV (%) 0.414 [6]	CrCL on CL 0.42 [26]	Diagnostic plots, bootstrap, visual predictive check	Prednisolone	[46]
	LN	0.5–1.5 g	Non-compartmental model	WinNonlin	MPA: T_{max} (h) 1.69 ± 1.86; C_{max} (μg/ml) 21.0 ± 16.2; Ctr_{12} (μg/ml) 4.06 ± 5.15; Lambda (h^{-1}) 0.11 ± 0.07; MRT (h) 16.3 ± 19.9; $AUC_{0–12\ h}$ (mg·h/l) 78.8 ± 74.1; $AUC_{6–12\ h}$ (mg · h/l) 33.2 ± 39.0; $Clr_{0–12\ h}$ (ml/min) 343 ± 200; $Ae_{0–12\ h}$ (mg) 4.81 ± 3.34; $Ae_{12–24\ h}$ (mg) 6.53 ± 9.10; MPA free (%) 2.56 ± 1.97 MPAG: T_{max} (h) 3.36 ± 3.56;	NS	Cr, CrCL, serum albumin, age, race, gender, steroid dose on MPA (Clr, CL/F, $AUC_{0–12\ h}$, $AUC_{6–12\ h}$) and MPAG (Clr, $AUC_{0–12\ h}$)	NS	NS	[54]

patients	Disease	Dose	Outline of PK model	Software	PK parameter estimates	Model variability	Covariates	Model assessment	Concomitant medication	Ref.
					C_{max} (μg/ml) 55.1 ± 42.7; Ctr_{12} (μg/ml) 28.2 ± 25.2; Lambda (h^{-1}) 0.08 ± 0.05; $AUC_{0–12}$ (mg · h/l) 518 ± 460; MPAG: MPA 7.09 ± 4.76; $Clr_{0–12}$ (ml/min) 53.5 ± 52.3; $Ae_{0–12\ h}$ (mg) 656 ± 310; $Ae_{12–24\ h}$ (mg) 441 ± 341; MPAG free (%) 9.30 ± 5.23					
	Severe LN	1–1.5 g/day MMF; 1.08–1.44 mg/day EC-MPS	Non-compartmental model	SPSS	MPA: $AUC_{0–12\ h}$ (mg h/l) 57.97 ± 29.38; C_{max} (mg/l) 19.43 ± 12.01; T_{max} (h) 1.54 ± 1.03 EC-MPS: $AUC_{0–12\ h}$ (mg · h/l) 42.44 ± 9.86; C_{max} (mg/l) 10.12 ± 5.13; T_{max} (h) 3.25 ± 2.52	NS	NS	NS	Prior to the start of MMF: prednisolone, cyclophosphamide	[55]
	SLE	1–3 g/day for ≥ 1 month	Non-compartmental model	Statistica Software, Analyse-it software	MPA: $AUC_{0–12\ h}$ (mg/h/l) 64.7 (38.2–82); C_{max} (mg/l) 16.1 (9.5–18.5); T_{max} (h) 1 (1–2); $C_{12\ h}$ (mg/l) 2.4 (1.5–4.1); MPAG: $AUC_{0–12\ h}$ (mg/h/l) 775.3 (475–1016); T_{max} (h) 2(2–3);$C_{12\ h}$ (mg/l) 32.1 (24.3–41.9)	BSV: mean MPA $AUC_{0–12\ h}$ (%) 44; mean MPAG $AUC_{0–12\ h}$ (%) 43	NS	Diagnostic plots	Corticosteroids	[56]
	Glomerulonephritis (SLE or vasculitis)	0.25–1.5 g	Non-compartmental model	SAS	MPA: C_{max} (μg/ml) 20.9 (17.9); T_{max} (h) 1.46 (1.48); Ctr_{12} (μg/ml) 4.11 (4.46); $AUC_{0–12\ h}$ (μg · h/ml) 66.3 (43.8); CL/F (ml/min) 305 (173); $AUC_{6–12\ h}$ (μg·h/ml) 24.1 (19.9); CL_R/F (ml/min) 3.74 (4.70); $T_{1/2}$ (h) 14.5 (18.7); $AUC_{6–12\ h}$/ $AUC_{0–12\ h}$ % 35.4 (12.2) MPAG: C_{max} (μg/ml) 63.9 (50.2); T_{max} (h) 3.02 (2.54); Ctr_{12} (μg/ml) 31.7 (27.8); $AUC_{0–12\ h}$ (μg · h/ml) 498 (433); $AUC_{6–12\ h}$ (μg·h/ml) 214 (191); CL_R/F (ml/min)	NS	MPA: Caucasian race and SCr on Ctr; UP: Cr and SCr on $AUC_{0–12\ h}$, $AUC_{6–12\ h}$, CL/F(1) and CL/F(2); weight on CL/F(2); weight and UGT2B7 Het on CLR/F MPAG: Caucasian race and	NS	NS	[57]

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patients	Disease	Dose	Outline of PK model	Software	PK parameter estimates	Model variability	Covariates	Model assessment	Concomitant medication	Ref.
					46.5 (45.9); $T_{1/2}$ (h) 16.9 (26.1); $AUC_{6–12\ h}$/ $AUC_{0–12\ h}$ % 39.7 (41.9) AcMPAG: C_{max} (μg/ml) 0.91 (1.08); T_{max} (h) 1.68 (1.65); Ctr_{12} (μg/ml) 0.28 (0.63); $AUC_{0–12\ h}$ (μg · h/ml) 3.88 (4.80); $AUC_{6–12\ h}$ (μg h/ml) 1.53 (2.12); CL_R/F (ml/min) 45.9 (53.4); $T_{1/2}$ (h) 10.4 (8.26); $AUC_{6–12\ h}$/ $AUC_{0–12\ h}$ % 0.37 (0.14)		SCr on $AUC_{0–12\ h}$ and $AUC_{6–12\ h;}$ female gender and SCr on CL_R/F Acyl-MPAG: Caucasian race and eClCr on $AUC_{0–12\ h}$; age and SCr on $AUC_{6–12\ h;}$ albumin and SCr on CL_R/F			
	SLE in remission maintenance	1.5 (1.0–2.0) g	Non-compartmental model	SPSS	NS	BSV: MPA free fraction (%) 70; MPAG free faction (%) 59.8	Metal medication and CrCL on MPA C_0; CrCL on MPAG C_0; serum albumin on MPA free fraction; serum albumin, metal medication and CrCL on MPAG free faction	NS	Prednisolone, metal medication	[58]
dren	cSLE	1 g	Non-compartmental model	WinNonlin, JMP	MPA without NSAIDs: C_{trough} (mg/l) 2.01 [2.52]; C_9 (mg/l) 2.33 [1.50]; $AUC_{0–12\ h}$ (h mg/l) 34.8 [24.7]; $AUC_{0–12\ h}$ (h mg/l per MMF 1 g dose) 35.9 [24.5]; CL/F (l/h) 29.2 [17.7]; C_9/C_{nadir} 2.4 [1.6]; $AUC_{6–12\ h}$ (h mg/l) 17.7 [16.3]; $AUC_{6–12\ h}/AUC_{0–12\ h}$ 0.47 [0.19] MPAG without NSAIDs: CL/F (l/h) 2.73 [1.94];	NS	NS	Diagnostic plots	NSAIDs	[59]

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patients	Disease	Dose	Outline of PK model	Software	PK parameter estimates	Model variability	Covariates	Model assessment	Concomitant medication	Ref.
					$AUC_{0–12}$ (h mg/l) 357 228; $AUC_{0–12}$ (h mg/l per MMF 1g dose) 370 230 MPA without NSAIDs: Ctrough (mg/l) 1.00 [0.57]; C_9 (mg/l) 1.36 [1.05]; $AUC_{0–12\ h}$ (h·mg/l) 30.0 [12.4]; $AUC_{0–12\ h}$ (h mg/l per MMF 1 g dose) 31.4 [11.9]; CL/F (l/h) 27.1 [10.8]; C_9/C_{nadir} 1.2 [0.4]; $AUC_{6–12\ h}$ (h mg/l) 11.7 [5.7]; $AUC_{6–12\ h}/AUC_{0–12\ h}$ 0.39 [0.11] MPAG without NSAIDs: CL/F (l/h) 2.34 [0.23]; $AUC_{0–12\ h}$ (h mg/l) 323 135; $AUC_{0–12\ h}$ (h mg/l per MMF 1 g dose) 346 133					
dren (16.9 ± 4	cSLE	1–3 g/day	Non-compartmental model	WinNonlin	MPA C_{max} (mg/l) 13.5 ± 6.83 (3.96–32.67); T_{max} (h) 0.92 ± 0.41 (0.33–1.52); $AUC_{0–12\ h}$ (mg h/l) 32 ± 18.1 (7.48–89.3); dose-normalized MPA $AUC_{0–12\ h}$ (mg h/l/g) 45 ± 24.1 (16.9–120.8); CL/F (l/h) 28 ± 13.7 (8.28–59.3)	NS	NS	NS	Prednisone, methylprednisolone, hydroxychloroquine, NSAIDs, antihypertensives	[60]
–28 years; 16.5 years)	cSLE	1–3 g/day	Six-compartment model including a gallbladder compartment for enterohepatic recycling and bile release time related to meal times	NONMEM, PDx-Pop, Xpose, R	$CL_{1\text{-}MPA}$ (l/h) 25.3; $V_{3\text{-}MPA}$ (l) 20.9; $CL_{2\text{-}MPA}$ (l/h) 19.8; $V_{4\text{-}MPA}$ (l) 234; CLM_{MPAG} (l/h) 2.5; FM-fixed 85%; FMPAG-fixed 65%; K_a (h^{-1})-fixed 1.5; MTT (h) 1.1; n 8.2; EHC-fixed 35%	BSV (%): CL_{1MPA} 48.6; V_{3MPA} 59.2; $CL_{2\text{-}MPA}$ 42.9; $V_{4\text{-}MPA}$ 60.0; CLM_{MPAG} 55.9 RUV: MPA (%) 41.2; MPAG (%) 45.4	Lack of any covariate relationship	Diagnostic plots, bootstrap, visual predictive check	Prednisone, methylprednisolone, hydroxychloroquine, NASIDs, antihypertensives	[48]
dren (4.7–16.7)	cSLE	728 ± 255 (300–1250) mg; 544 ± 175 (217–998)	One-compartment model with first-order elimination and absorption	In-house software, R	V_c/F (l) 24.8 ± 13.5; CL/F (l/h) 19.2 ± 13.2 l/h	NS	None	Diagnostic plots, visual predictive check	NS	[50]
	Autoimmune with 23 SLE and 21 vasculitis	2 mg/day	Non-compartmental model	Analyse-it	$AUC_{0–12\ h}$ (mg h/l) 49 (33–75); C_0 (mg/l) 2.5 (1.6–3.7); $C_{12\ h}$ (mg/l) 2.1 (1.7–3.2)	NS	NS	NS	Corticosteroid	[61]

patients	Disease	Dose	Outline of PK model	Software	PK parameter estimates	Model variability	Covariates	Model assessment	Concomitant medication	Ref.
	Severe LN	1.5 g/day	Non-compartmental model	GraphPad	Average MPA $AUC_{0-12\ h}$ (mg h/l) 66.4 [25.3]; average plasma MPA CL (mg/l) >13 (12.58–19.74)	NS	NS	NS	Prednisolone	[62]

e; AUC: Area under the plasma drug concentration-time curve; BSV: Between-subject variability; C_0: Trough plasma concentrations; C_9: MPA concentration at 9 h; CL: Apparent oral clearance; Clr: renal clearance; CLR/F: Apparent renal clearance; C_{max}: Maximum (or peak) serum concentration; C_{nadir} Nadir concentration between the e clearance; Ctr: Concentration trough; Ctr_{12}: Mean MPA trough at 12 h; DGB: Duration of gallbladder opening; EHCP: % MPA recycled into the body; F_{fast}: Part of dose compartment; FMPAG: Fraction of renal eliminated MPAG; K_{12}: Absorption rate constant; K_{51} : Rate constant between gallbladder and gastrointestinal compartment; K_a: te of elimination (Ke); LN: Lupus nephritis; MPA: Mycophenolic acid; MPAG: 7-O-MPA-glucuronide; MRT: Mean residence time; MTT: Mean transit time into first depot linear mixed-effects modeling; Prop: Proportional error; Q: Intercompartmental clearance; Q/F: Apparent intercompartmental clearance; RUV: Residual (unexpected) e; SLE: Systemic lupus erythematosus; T1/2: Half-life; T_{gb1}: Time of first opening gallbladder compartment; T_{lag}: Lag time between intake and start of absorption; T_{lag}, ; T_{lag}, long: Lag time long absorption; T_{max}: Time to maximum concentration; UP:Cr: Urinary protein to creatinine ratio; V_1/F: Apparent volume of distribution in the parent volume of distribution in MPA central compartment; V_3/F: Apparent volume of distribution in MPA peripheral compartment; V_4/F: Apparent volume of distribution in : Volume of distribution in MPA peripheral compartment; V_C/F: Apparent of distribution of the central compartment; V_C: Volume of distribution of the central compartment; bution after oral administration; V_p: Volume of distribution of the peripheral compartment; θ: Population average CL/F for individuals with different mutant genotypes.