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A Review of the Pharmacokinetics of Cyclosporin

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1. Introduction

Cyclosporin (cyclosporin A, CsA) is a potent immunosuppressant drug that is widely used to prevent graft rejectionin transplantation medicine and to treat several autoimmune diseases. It is a cyclic polypeptide of fungi origin consisting of 11 amino acids (Figure 1)[1].Unlike some non-selective immunosuppressant drugs such as methotrexate or azathioprine, CsAselectivelytargets the proliferation of helper T-cells but not the suppressor T-cells, and thus suppresses the T-cytotoxic lymphocytes cell proliferation and formationwithout causing myelotoxicity[2].CsA however, suffers from a narrow therapeutic index and a great pharmacokinetic (PK) intra and inter subject variability, especially in the absorption phase, which greatly complicate therapy[3]. This means thateven at the same dose ratewithin a recommended range,CsAtherapy could be sub-therapeutic for certain patients leading to therapy failure and/or graft rejection, or could be toxic for other patients causing serious irreversible kidney damage[4]. Therefore, monitoring the PK profiles of patients as part of routinely carried out therapeutic drug monitoring becomes very vital for the success ofCsA therapy.

CsA is indicated for the prevention of rejection following organ transplantations including heart, lung and kidney, for the treatment of graft-vs-host disease with bone marrow transplant, and for the treatment of various autoimmune conditions such as rheumatoid arthritis, nephrotic syndrome and psoriasis[5].It is available for intravenous (IV) infusion but the oral administration as soft gelatin capsules or solution is usually more commonly used. The original CsA product, Sandimmun® (Novartis AG, Basel, Switzerland), is an oil-in-water emulsion, however a newer micro-emulsion formulation, Neoral® (Novartis AG, Basel, Switzerland)which improves the oral bioavailability of CsAwas also developedand approved for use[6]. The two formulations are not bioequivalent and cannot be used interchangeably[7]. Here we review the PK of CsA.

2. Pharmacokinetic Properties of Cyclosporin

2.1. Absorption

Absorption is a critical component of the PK of CsA administered orally.The absorptionis slow and incomplete, and takes place predominantly in the upper part of the small intestine [8]. Therefore, the length of the small bowel is an important determinant of the oral CsA dosage requirement for patients with reduced absorptive surface area including children [8, 9]. Moreover, thesmall window of absorptionmakes modified release formulationsnot a feasible option for CsA.

High inter-subject variability has been reported in studies which evaluated oral CsA[10, 11, 12].The absorption half-lifemeasured ranged from 0.5 to 2 h and a lag time up to 1 h in absorption hasbeen reported in some patients [13]. The peak concentration (C_{max}) was reached after an average time (T_{max}) of 3.8 h (a range of 1-8 h) post-dose, and in some studies, a second peak in the concentration-vs-time curve was observed (which in some cases was as high as or higher than the first peak) in a proportion of patients at about 5-6 h following the first peak[14, 15]. The reason behind the second peak

is notclear, but there are reports of patients having a similar second peak that is attributed to bile related enhancement in absorption following a meal taken during the absorptive phase [14]. The absolute bioavailability (F) of oral CsA is low, and was estimated by Beveridge et al to be 30% (range 10-60%) for theoriginal CsA formulation[16]. Absorption of oral CsAcan be improved by the dispersion of the CsA solution in a drink that the patient prefers.

The Neoral® micro-emulsion formulation considerably improved the absorption and absolute bioavailability of oral CsA[17].Kovarik et al reported an increase in absorption of the micro-emulsion CsAin kidney transplant patients as measured by an increase in the area under the concentration-vs-time curve (AUC) by about 44% and the C_{max} by 73% compared to the original formulation[18].Drew et al found similar results in healthy volunteers, which included an increase in AUC of about 49%[19]. Both studies did not observe a significant change in T_{max}. The improvements in CsA bioavailability with the micro-emulsion formulation was estimated to be in the range of 3.7-6.5 folds greater than that achieved with the standard formulation [17, 20].

There is evidence that a PK model which assumes a zero-order absorptionin the upper part of the small intestine under conditions of saturation can provide a superior description of the data in humans than would a first order model[8]. This is substantiated by the two observations, i)that small doses of CsA produceunproportioned high blood concentrations, and ii) that small episodes of diarrhea which decrease the transit time at the site of absorption lead to low CsAblood concentrations[21].Reymond et al compared PK parameters across three different oral doses of Sandimmun®CsA (350 mg, 700 mg, and 1400 mg) given to healthy volunteers and concluded that both absorption and disposition of CsA followed nonlinear dose-dependent kinetics[22]. However, this nonlinearity was not observed with the micro-emulsion formulation, Neoral®, over the dose range (300-800 mg) [23].

The decrease in CsA blood concentration following diarrhea suggests an effect for gut motility on the absorption of CsA[24]. A number of other factors influence the absorption of CsA when given orally. The bile flow is one of these factorswhich is expected sinceCsA isa highly lipid soluble compound. This influence wasseen in reported caseswhere an increase in trough CsA concentrations was found following the clamping of the T tube, and the evidence attributed that to an increase in CsA solubilisation at the site of absorption due to improvements in bile flow into the gut [25].The co-administration of CsA and bile salts was found to significantly improve the CsA bioavailability[26]. The influence of bile and the fact that the absorbance of CsA is represented by a zero order model suggests food as a factor that would influences absorption of CsA. The evidence, however, to the effect of food on CsA absorption has been conflicting[27]. Gupta et al observed an increase in C_{max} and in the bioavailability of CsA in healthy volunteers following oral administration with a fat loaded meal as compared to taking it on a fasted state[28]. Another study showeda significant increase in C_{max} and AUCof CsA with standard meal following oral administration in renal transplant patients [29]. However, some other studies found no significant effect for food on CsA absorption[27]

2.2. Distribution

The concentration-time profile of CsA following intravenous and oral administration has been found to be best described by multi-compartment modelsincluding two- and three-compartment models, however a two compartment model has been found to accurately represent the data and has been adapted by many published studies [30]. Follath et al used three compartments to model the disposition of CsA following

a short IV infusion, and observed a fast initial decline with a half-life of 0.10±0.03 h followed by abiphasic disposition with half-lives of1.08±0.25 h and15.8±8.4 h, whichindicates that CsA can easily diffuse through various biological membranes[31].

CsA, being highly lipophilic, distributes widely into blood, plasma and tissue components.Based on an in-vitro study, it was found that about 30-40% of the CsA in blood lies in plasma, 40- 50% in the erythrocytefraction, and10-20% in the leukocyte fraction[32].However, the distribution varies with temperature, drug concentrations, hematocrit, and plasma lipoproteins [33]. Moreover, CsA increases lipoprotein concentrations, thus affecting its own distribution [34].In plasma, CsA is mostly bound tolipoproteins (about 80%). The unbound fraction of the drug measured in plasma (f_u) ranged between 0.04-0.12 in renal transplant patientswhich indicates extensive protein binding [35].In the body, CsAdistributes into many cells and tissues [36], but the accumulation is more in organs rich in fat including liver, adipose tissues, and lymph nodes[33]. The lymph concentrations of CsA were found to be approximately 40–60% of the corresponding blood concentrations in rats [37]. Other tissues such as pancreas, kidneys, and adrenal glands contain higherCsA concentrations than serum [38].CsA, however, has restricted permeability across the blood-brain barrier[33].The apparentvolume of distribution (Vd)of CsA varies according to type of allograft and disease state.Aweeka et al reporteda CsAvolume of distribution at steady state (Vss) value of 1.9 L/kg in blood (2.4 L/kg in plasma) in kidney pre-transplant subjects, and a value of 1.2 L/kg in blood (1.2 L/kg in plasma) in healthy subjects,and suggested alteration in protein binding as a cause for the increase in Vss[39]. Yee et al found that Vss correlated negatively with age in bone marrow patients with Vssvalues of 34.4 L/kg in patients below 11 years, 20.6 L/kg for patients 11-40 years, and 4.7 L/kg for patients over 40 years[40].

2.3. Metabolism

CsA is extensively metabolised in the liver with biliary excretion being the major route of metabolite elimination [41]. An estimated 50% of the CsA dose given is extracted from the blood during the first pass through the liver [42]. The key catalyst for the biotransformation of CsA in the liver is the cytochrome P-450 III-A enzyme subfamily (CYP3A) found in the endoplasmic reticulum of liver cells, and is also found in tissues of other organs including in the cells of the gut wall [43]. There is evidence that the gut wall is also involved in the first pass metabolism of CsA and this contributes to its low bioavailability following oral dosing [44]. Over 30 metabolites have been suggested for CsA and Maurer et al have isolated 9 of these[41, 45]. The levels of three of the primary metabolites, themonohydroxylated metabolites M1 (15%) and M17 (the predominant metabolite in man, 55%) and the N-demethylated metabolite M21, have been found to correlate with the amount of CYP3A in the liver[46]. The metabolites, which could be found in concentrations exceeding those of CsA in the blood of transplant patients,are more hydrophilic than CsA, mostly show a minor immunosuppressive activity (<10% of that of CsA), and are less nephrotoxic than CsA[47, 45, 48]. However, the metabolite combinations have additive and synergistic effects [45, 48]. These metabolites show different distribution than CsA and eliminate more easily from the gut or kidney. Thus, metabolism is an important factor when considering PK and drug interaction of CsA.

2.4. Elimination

The primary route of CsA elimination is by metabolism in the liver and excretion of the drug and metabolites by the biliary system[49]. Venkataramanan et al observed that only small amounts of intact

CsA is excreted in bile in liver transplant patients, but to the contrary, large amounts of CsA plus metabolites are excreted in bile [49]. These results suggest that CsA metabolites, but not the intact CsA, undergo enterohepatic recycling, at least, in this patient group, but most of the drug is ultimately excreted in the feces. CsA is also eliminated through urinary excretion, however, to alesser extent. In human, it is estimated that less than 10% (with reports of as little as 3%) of the administered dose is excreted in the urine and only fraction of that being as unchanged drug[50].

CsA elimination is found to follow a first-order kinetics with most doses considered, and thus Vd and the systemic clearance (Cl) are independent of the doses [42]. The exception to this is when high doses, over 6 mg/kg/h, are given by fast IV infusions,whence due to saturation of the hepatics uptake system, elimination kinetics become of zero-order. Estimates of the Cl reported in the literature show great interpatient variability. Ptachcinski et al found that,following a CsA IV infusion of 2.1 mg/kg over 2 h, healthy subjects exhibited a mean distribution half-life of 0.45 h(range 0.23-1.53 h), a mean terminal half-life of 6.2 h (range 4.7-12.7 h), a first-order elimination rate constant (k_{10}) of 1.34±1.03 h^{-1}, a Cl of 3.9 ml/min/kg (range, 2.9-5.5ml/min/kg) and a Vss of 1.25±0.30 L/kg[51]. These values which are based on a 2 compartment PK model, include a shorter half-life, a lower Cl, and a smaller Vss when compared to data reported for transplant patient populations, and demonstrate the extent of interpatient variability.

CsA is a drug with low to moderate hepatic extraction ratio (ER). Wu et al reported ER values of 0.25±0.06 in healthy volunteers and of 0.27±0.10 in kidney transplant patients[52]. Therefore, the hepatic clearance of CsA is "enzyme-limited" and is affected by both the unbound fraction of CsA in the blood (f_u) and the unbound intrinsic clearance(Cl'_{int})[53].Various factors alter CsA elimination. Some of these factors and their effects are provided in Table1.

3. The Importance of CyclosporinPharmacokinetics inClinical Use

For effective management of therapy for patients onCsA, it is imperative for health care providers to have an insight on the internal exposure of CsA and be able to predict the concentrations that reach the site of action to ensure efficacy and safety. Pharmacokinetic studies as part of regular therapeutic drug monitoring (TDM) allow health care providers achieve that and provide and optimize individualized treatment plans. There are a number of reasons why such PK studies become an obvious necessity for patients on CsA. We list a few next.

3.1. The Inter- and Intra-Individual Variation in PK

A major pharmacokinetic challengein the CsA therapy is that the drug exposure, as defined by AUC, varies widely between patients receiving the same dose of drug. In fact, great variability is observed in many PK parameters with CsA, and this has been partially attributed to inter-individual variations in the activity of the enzyme CYP3A4[54].The bioavailability of CsA following oral dosing of the original Sandimmun® has been shown to be low around 30%, but the range among different patients has been found to vary as much as 2% to 89%[42]. The volume of distributionis another PK parameter that shows inter-individual variation. Using a non-compartmental analysis of whole blood from different groups, Clardy et al found Vss values of 7.9±5.1L/kg [55], with high inter-individual variations.Differences in clearance have also been reported and have been attributed to inter-individual variation in CsAmetabolism.The variations that have been observed between different patients, have also been observed for the same patients at different times [56]. The newer Neoral® formulation has improved the

bioavailability of CsA, but it still shows similar inter-individual variations as the original formulation [4].

Several attempts have been made to understand the substantial inter-individual variation in CsA PK asbeing potentialresults of the polymorphic expression of the CYP3A enzyme. However, research on the pharmacogenetic variations have not been consistent and has shown no pharmacological impact of the polymorphism on CsA PK[57]. Von Ahsen et al attempted to correlate a polymorphism in exon 26 (C3435T) of the multidrug resistance-1 (MRD-1) gene (MDR-1 C3435T) or a polymorphism in the CYP3A4 promoter region ("variant" allele CYP3A4-V)with theintestinal P-glycoprotein (P-gp) concentration in 126 renal transplant recipients. They found that both polymorphisms were not major determinants of CsA efficacy[58]. Hesselink et al also found no correlation between polymorphisms of the CYP3A4 (CYP3A4*1B and*3),CYP3A5 (CYP3A5*3 and *6), and MDR-1 (MDR-1 C3435T) genes and dose adjusted CsA trough levels. They, however found some correlations with tacrolimus, another calcineurin inhibitor[59].These results highlight the need for studies which try to predict the combined effect of the many polymorphisms.

3.2. Narrow Therapeutic Index

CsA is classified as a critical-dose drug with a narrow therapeutic window and there is evidence that a clinically significant change in efficacy or toxicity occurs with small changes in dose or concentration[60]. This was noted by Lindholmet al, who found a significant difference in the percent of one year rejection-free kidney transplant patients at three steady state CsA concentration levels [61]. In the same study, the daily dose administered did not correlate with the outcome of percent one-year rejection free. The appropriate CsA therapeutic range must be determined for eachpatient taking into account the type of assay used, the sample matrix, the patient's lipid and hematocrit profile, the patient's risk factors, and the patient'sother medications. An important note to consider, is that while there are different oral formulations of CsA that are available including some generic ones, these formulations at equal doses may not provide equivalentCsA concentrations and may require dose adjustments in order to have concentrations within the therapeutic window [62].

3.3. Renal Adverse Events

A number of serious side effects have been reported with the use of CsA, but its nephrotoxicity is the most importantone that limits its use, followed by hypertension [63]. Krupp et al found that among 3514 renal transplant recipients, over 54% experiencedadverse effects with CsA related to renal dysfunction [64]. CsA can cause a dose dependent acute toxicity associated with a reduction in renal plasma flow and glomerular filtration rate along with an increase in serum biochemical parameters including creatinine and urea[65]. These effects are reversible, and by regular PK profiling and carefully monitoring the CsA concentrations and the levels of these biochemical parameters and adjusting the CsA doses accordingly, renal impairment can be avoided. Myer et al found that a CsA AUC of over 13 mg.h/L correlated with nephrotoxicity, whereas a value of 8 mg.h/L correlated with protection from rejection in first renal transplant recipients [66]. On the other hand, these acutetoxicities can progress and lead to structural damage of the kidney, especially when high CsA doses are used[67].

3.4. Difficulties in Measuring Clinical Outcome

One of the challenges with CsA treatment, especially when given as a prophylaxis to prevent rejection following organ transplantations, is the difficulty in measuring the clinical outcome. The lack of intermediate clinical signs with proven correlation with immunosuppression associated with CsA makes it difficult to quantify the efficacy of the treatment[42].In fact, the first sign of inefficacy could be a rejection of the organ, while signs of toxicity could be serious irreversible damages to the kidneys and other organs. Therefore, PK monitoring should be employed regularly to compensate for the lack of such clinical markers by maintaining CsA concentrations in a range that is found to be efficacious and safe for the patients.

4. Pharmacokinetics and Pharmacodynamics

Several pharmacodynamics (PD) studies have examined the biochemical and physiological effects of CsA on the body under various conditions.CsA is a calcineurin inhibitor that binds to the immunophilincyclophilinand causes inhibition of transcription of interleukin-2 (IL-2) and several other cytokines, mostly in T-helper lymphocytes[14]. This reduces the production of various cytokines and inhibits the activation and maturation of various cell types, including those involved in the autoimmune response.Therefore, the effect of CsAon calcineurin-phosphatase activity was chosen for many of the CsA PD studies.

Brunel et al used a PK/PD model to establish an effective and therapeutic CsA concentration range in renal transplant patients[68]. Theyobserved a strong correlation betweenCsAblood concentration at a single point 2 hours (C_2) post-dose and the AUC of the first 4 h (AUC_{0-4}). Such strong correlation was not established for the trough concentration. This observation was in line with earlier attempts to simplify CsA TDM by reducing the number of blood sampling points needed to monitor CsA[4]. Moreover, they found that CsAmonotherapy at a mean dose of 2.6±0.9mg/kg/dayshowed a significant reduction of 89.6% of the calcineurin activity, of 56.1% in IL-2 production, and of 72.1% in interferon-gamma (IFN-γ) production, compared to healthy controls. Based on amaximal drug effect (Emax) inhibitory sigmoidal model, they concluded that a C_2 of 279 ng/ml was required for a 50% maximal effect (EC_{50}) which was inhibition of IL-2 and IFN-γproductionwhile a C_2 of 384 ng/ml resulted in a degree of inhibition of calcineurin activity and production of IL-2 and IFN-γ that is safe and is associated with a lack of rejection episodes [68].Fukudo et also used an Emax PD model to study CsA using calcineurin activity as a measure of effect, and found comparable CsA concentrations that provided 50% effect [69].On the higher extreme, they observed a steepdecline in calcineurin activity with increase in CsA concentrations, but a plateau was reached beyond whichCsAexerted no additional effect at a threshold blood concentrations of approximately 700 ng/ml. Their results were similar to those obtained in another PD study of CsA where the effect measured was the inhibition of IL-2 [70].

PD models have also helped understand the effect of CsA in special populations. Marshall et al conducted an in-vitro study in which the effect of CsA at concentrations ranging from 0-5000 ng/mL were studied on the inhibition of peripheral blood monocyte proliferation and IL-2 production in blood samples from subjects ranging in age from 2 months to 39 years. Using the Emax model, they found that three of the four age groups considered were similar with respect to mean Emax and EC50, but the infant group (0-1 year) showed a 2-fold lower EC50 in relation to inhibition of peripheral blood monocyte proliferation and 7-fold in relation to inhibition of IL-2 production when compared to adults.

Their results highlight the importance of including age as a factor when immunosuppression with CsA is considered in pediatrics.

Stein et al used a PK/PD model to explore if a difference in CsA effect could explain the lower renal allograft survival reported in African Americanscompared with caucasian patients[71]. They considered testing both the emulsion and the micro-emulsion formulations of CsA in the study in patients from both races and used the inhibition of IL-2 production in whole blood drawn 4 hours after CsA was administered as a PD measure of effect. Their results revealed comparable PK and PD profiles between the two races which suggest that environmental rather than genetic factors could explain the lower renal allograft survival in African Americans [71].

PK/PDstudies have also helped understand thetoxicity associated with CsA. Using the Emax model, Grześk et al studied the CsA effect on the reactivity of vascular smooth muscle cells[72]. Their results showed an increase inextracellularcalciuminflux to thecytoplasm and highlighted the importance of peripheral regulation of protein kinaseC in the hypertension due to CsA.

5. Interactions Altering Cyclosporin Pharmacokinetics

5.1. Drug Interactions

A rangeof drugs have been recognised to interact with CsA and potentially lead to blood CsA concentrations that fall outside the safe and therapeutic range or that add to its nephrotoxicity.These interactions occur as a result of alteration of CsA PK parameters and/oralteration of the physiological or pharmacological effect[73].

Calcium channel blockers, often used for the treatment of hypertension that is high among CsA users, are suggested to increase the CsA concentrations and potentiate its immunosuppressive effect[74].Weir et al found that when verapamilwas combinedwith CsA,several CsA PK parameters were altered and around half of the CsAconcentration was required to achieve the same degree of immunosuppression as that produced with CsA alone[74]. Smith et al also observed a change in the PK of CsAwhen combined with diltiazem, including a significant reduction in blood Cl andVd with no change in renal effect[75]. The change in these PK parameters, resulted in a reduction of the CsAoral dosage regimen needed to achieve a target blood concentration.However, two other calcium channel blockers, nifedipine and nitrendipine, have been reported not to interact with CsA[73]. Other drugs have also been found to increase the CsA concentrations. These include the two macrolide antibiotics erythromycin and josamycin, several azole antifungal drugs including ketoconazole, and many other drugs.The mechanism behind the increase in CsA concentration is attributed to an improvement in the absorption of CsA given orally along with these drugs and/or to a disruption in the CsA metabolism[75].

Drugs can also interact with CsA and lead to lower CsA blood concentrations. The anticonvulsantphenobarbitone was found to decrease the CsA concentrations in bone marrow transplant patients to levels which could be undetectable even with high CsAdoses [76]. Similar reductions in CsA concentrations were reported when co-administered withother anticonvulsants including, carbamazepine in renal transplant patients [77], and phenytoin in heathy patients [78]. In the latter study, phenytoin significantly decreased the C_{max} and the AUC of CsA and two of its metabolites, M17 and M18. There are other drugs which cause similar reduction in CsA concentrations including rifampin, nafcillin,

octreotide, and sulfonamides and trimethoprim and the mechanism of the interaction is suggested to be acceleration of CsA metabolism [78, 79].

5.2. Herbal Extract and Food Interactions

CsA has been found to interact with St John's wort (SJW),an herbal extract that is used in the treatment of mild depression. Bauer et al observed that the co-administration of SJW with CsA for two weeks in renal transplant patients resulted in a decrease of CsA concentrations amounting to over 40% decrease in AUC_{0-12}[80]. This decrease startedrapidly from the third day of treatment and a 60% dose increase was required to achieve the therapeutic target.Moreover, the SJW treatment also effected the PK of the CsA metabolites.Grapefruit juice has also been shown, in a number of studies, to interact with CsA when given orally. Ducharme et al found a significant increase in the CsAabsolute bioavailability of about 62% with grapefruit juice [81]. No effect was observed for grapefruit juice when CsA was given intravenously. Considering the extensive variability of CsA absorption, both SJW and grapefruit juice should be avoided with CsA therapy.

6. Cyclosporin in Special Patient Groups

The disposition of CsA in human has been clinically found to be influenced by age, gender, and even the ethnicity of the patients. CsAclearance, for example, is influenced by the age of the patient. In pediatric patients, twice as high clearance is observed in pediatric liver, kidney, and bone marrow transplant patients than in adults[82, 10, 83]. This high clearance is due to faster removal of the drug from the body, and therefore, pediatric patients require higher doses which may be given in more frequent intervals. Adult patients over 40 years showed 50% lower Cl and 25% lower Vssvalues compared to patients 40 years or below in bone marrow transplantation [83].Female patients are found to clear CsA more rapidly compared to males, and have a higher Vd[11]. The ethnicity of the patients can also have an effect on the CsA disposition. The bioavailability ofCsA(Sandimmun® and Neoral®) has been found to be significantly lower in African American patients than in Caucasians[84].

CsA clearance is affected by patient's disease states. Patients with congestive heart failure, may experience alteration in the hepatic blood flow, which has been found to decreaseCsA clearance by as much as 50% [85]. Liver diseasemay also alterCsA clearance. Patient with cirrhosis have been reported to have low CsA clearance, which amounts to about half of that in liver or kidney transplant patients [86]. Conditions which alter the renal clearance should not alter CsAclearance since only a small proportion ofCsA is excreted in urine.

7. Population Pharmacokinetics

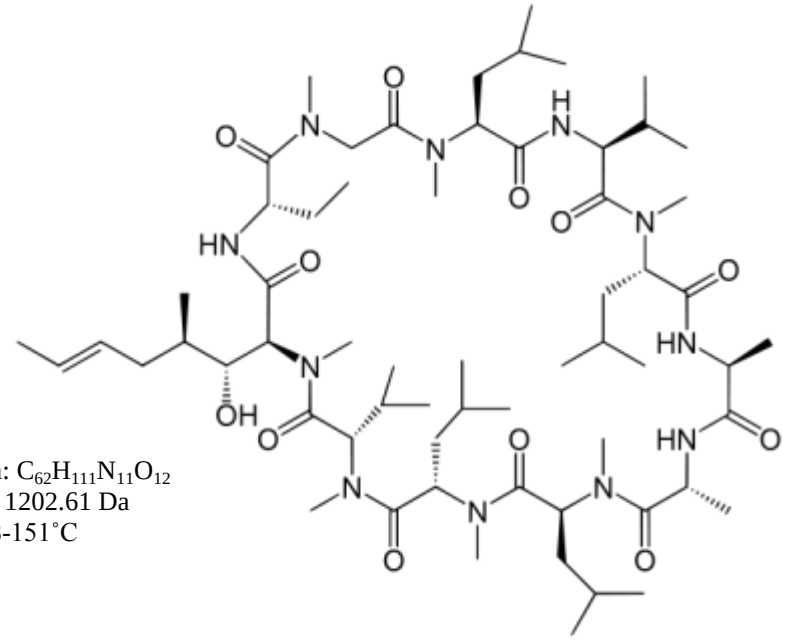
Several challenges face classical PK studies of CsA,including extensive variability in PK parameters, difficulties in obtaining enough patients that represent the population, difficulties in obtaining sufficient blood samples per patient, and difficulties in following the patients for long periods. Population PK studies, which rely on different statistical techniques such as mixed-nonlinear effect models, have complemented classical PK studies and addressed these difficulties and allowed the use of sparse data from a larger number of patient group with few samples per patients[87]. These models helped identify different covariates which help prescribers in individualizing and optimizing CsA treatment plans.

8. Advanced Cyclosporin Delivery Systems

Despite being a potent immunosuppressant, the increased use of CsA has been hindered by its safety profile. Several approaches have been proposed to reduce its side effects, including the co-administration of other agents that reduce its toxicity, or the use of more advance drug delivery systems such as lipid- or polymer- based nanocarriers[88]. The latter approach has been more hopeful, and extensive research has already been carried out with promising results. Aliabadi et al have developedmethoxy poly(ethylene oxide)-*b*-poly(ε-caprolactone)based CsA micellar formulation that solubilizes CsA, confines it to the blood and restricts its access to tissues, and thus potentially reduces CsA related toxicity[89]. In-vivo and in-vitro studies showed the micellar formulation to have equivalent immunosuppressant activity to Sandimmun®[90].

9. Conclusions

CsA is a potent immunosuppressant that has been effectively used to prevent graft rejection in transplantation medicine and to treat several autoimmune diseases.The extensive variability of CsA kinetics along with its narrow therapeutic index make regular PK profiling of patients as part of routinelycarried out therapeutic drug monitoring very important to ensure safety and efficacy of the treatment. Classical as well as population based PK studies provide information that aid in that regard. It is anticipated that CsA will continue to be extensively used, especially with the emergence of advanced delivery systems which target specific sites of action and reduce its toxicity.



Molecular formula: $C_{62}H_{111}N_{11}O_{12}$
Molecular weight: 1202.61 Da
Melting point: 148-151˚C

Figure 1. Structure of cyclosporin

Table 1. Factors which affect cyclosporin elimination

Factor	Observation
Age	▪ Pediatric patients clear CsA more rapidly compared to adults and thus require larger and more frequent doses. ▪ CsA Cl is 1.7-2 times higher in pediatric liver and kidney recipients compared with adults [82, 96].

	▪ Patients over 40 years oldshow 50% lower Cl and 25% lower Vss compared to patients 40 yearsor younger in bone marrow transplantation [83].
	▪ Higher CsA Cl was observed in patients less than 45 years old than patients over 45 years[11].
Gender	▪ Female patients clear CsA more rapidly compared to males, and have a higher Vd[11].
Race	▪ African Americans women clear CsA slightly faster than Caucasian women (Cl, 5.5 ± 1.2 vs. 4.1 ± 0.6 mL/min/kg) [84].
Liver disease	▪ CsA clearance is impaired in patients with liver disease. In renal transplant patients, impairment of liver function resulted in a reduction of Cl to 0.525 L/h/kg compared to the 0.786 L/h/kg found in patients with normal liver function, and a 30 to 50% increase in AUC [97].
Food	▪ Both Cl and Vd increase with high fat meals [53].
Body Weight	▪ Obese recipients of renal allografts dossed according to their actual body weight, but not according to their ideal body weight, show a trough concentration which is around twice that in non-obese patients [98].
Dosage Regimen	▪ The timing and frequency of dosing may alter CsA elimination. ▪ CsA clearance is indicated to follow a diurnal variation, and Browne et al have developed a diurnal dosing which improved therapy [99].
Other Drugs	▪ Various drugs, especially those which cause a change in the activity of the hepatic-drug metabolising system, have been reported to interact with CsA and alter its kinetics including elimination [100].

Bibliography

[1] J. A. Borel, C. Feurer, H. U. Gubler and H. Stähelin, "Biological effects of cyclosporin A: a new antilymphocytic agent," *Agents and actions*, vol. 43, no. 3-4, pp. 179-186, 1994.

[2] A. Von Wartburg and R. Traber, "Chemistry of the natural cyclosporin metabolites.," in *ciclosporin*, Basel, Karger, 1986, pp. 28-45.

[3] B. D. Kahan, P. Keown, G. A. Levy and A. Johnston, "Therapeutic drug monitoring of immunosuppressant drugs in clinical practice," *Clinical therapeutics*, vol. 24, no. 3, pp. 330-350, 2002.

[4] B. D. Kahan, "Therapeutic Drug Monitoring of Cyclosporine: 20 Years of Progress," *Transplantation Proceedings*, vol. 36, no. Suppl 25, pp. 378S-391S, 2004.

[5] P. R. Beauchesne, C. N. S. C and K. M. Wasan, "Cyclosporine A: A Review of Current Oral and Intravenous Delivery Systems," *Drug Development and Industrial Pharmacy*, vol. 3, no. 211-220, p. 33, 2007.

[6] S. Noble and A. Markham, "A Review of the Pharmacokinetic Properties, Clinical Efficacy and Tolerability of a Microemulsion-Based Formulation (Neoral®)," *Drugs*, vol. 50, no. 5, pp. 924-941, 1995.

[7] M. Medeiros, J. Pérez-urizar, M. A. and G. Castañeda-hernández, "Limited sampling model for area-under-the-curve monitoring in pediatric patients receiving either Sandimmune® or Neoral® cyclosporin A oral formulations," *Pediatric transplantation*, pp. 225-230, 1999.

[8] J. Drewe, C. Beglinger and T. Kissel, "The absorption site of cyclosporin in the human

gastrointestinal tract," *British journal of clinical pharmacology,* vol. 33, no. 1, pp. 39-43, 1992.

[9] P. F. Whitington, J. C. Emond, S. H. Whitington, C. E. Broelsch and A. L. Baker, "Small-bowel length and the dose of cyclosporine in children after liver transplantation," *New England Journal of Medicine,* vol. 322, no. 11, pp. 733-738, 1990.

[10] R. J. Ptachcinski, R. Venkataramanan, J. T. Rosenthal, G. J. Burckart, R. J. Taylor and T. R. Hakala, "Cyclosporine kinetics in renal transplantation," *Clinical Pharmacology & Therapeutics,* vol. 38, no. 3, pp. 296-300, 1985.

[11] B. D. Kahan, W. G. Kramer, C. Wideman, S. M. Flkciiner, M. I. Lorber and C. T. Van Buren, "Demographic factors affecting the pharmacokinetics of cyclosporine estimated by radioimmunoassay," *Transplantation,* vol. 41, no. 4, pp. 459-464, 1986.

[12] J. Grevel, E. Nüesch, E. Abisch and K. Kutz, "Pharmacokinetics of oral cyclosporin A (Sandimmun) in healthy subjects," *European journal of clinical pharmacology,* vol. 31, no. 2, pp. 211-216, 1986.

[13] M. P. Ducharme, L. Verret, D. Brouillette and G. Sirois, "Ability of a first-pass pharmacokinetic model to characterize cyclosporine blood concentrations after administrations of Sandimmune or Neoral formulations," *Therapeutic drug monitoring,* vol. 20, no. 2, pp. 165-171, 1998.

[14] D. Faulds, K. L. Goa and P. Benfield, "Cyclosporin," *Drugs,* vol. 45, no. 6, pp. 953-1040, 1993.

[15] R. Beukers, S. De Rave, J. W. Van den Berg and S. W. Schalm, "Oral pharmacokinetics of cyclosporin a in 67 patients with primary biliary cirrhosis and patients with skin diseases," *Aliment Pharmacol Ther,* vol. 6, no. 4, pp. 459-468, 1992.

[16] T. Beveridge, A. Gratwohl, F. Michot, W. Niederberger, E. Nuesch, K. Nussbaumer, P. Schaub and B. Speck, "Cyclosporin-A-pharmacokinetics after a single dose in man and serum levels after multiple dosing in recipients of allogeneic bone-marrow grafts," *Current Therapeutic Research-Clinical and Experimental,* vol. 30, no. 1, pp. 5-18, 1981.

[17] A. K. Trull, K. K. Tan, L. Tan, G. J. Alexander and N. V. Jamieson, "Absorption of cyclosporin from conventional and new microemulsion oral formulations in liver transplant recipients with external biliary diversion," *British journal of clinical pharmacology,* vol. 39, no. 6, pp. 627-631, 1995.

[18] J. M. Kovarik, Z. Kallay, E. A. Mueller, J. B. van Bree, W. Arns and E. Renner, "Acute effect of cyclosporin on renal function following the initial changeover to a microemulsion formulation in stable kidney transplant patients," *Transplant international,* vol. 8, no. 5, pp. 335-339, 1995.

[19] J. U. Drewe, R. E. Meier, J. A. Vonderscher, D. E. Kiss, U. L. Posanski, T. Kissel and K. Gyr, "Enhancement of the oral absorption of cyclosporin in man," *British journal of clinical pharmacology,* vol. 34, no. 1, pp. 60-4, 1992.

[20] S. Friman and L. Bäckman, "A new microemulsion formulation of cyclosporin," *Clinical pharmacokinetics,* vol. 30, no. 3, pp. 181-193, 1996.

[21] J. Grevel, "Absorption of cyclosporine A after oral dosing," *Transplantation proceedings,* vol. 18, no. 6 Suppl 5, pp. 9-15, 1986.

[22] J. P. Reymond, J. L. Steimer and W. Niederberger, "On the dose dependency of cyclosporin A absorption and disposition in healthy volunteers," *Journal of pharmacokinetics and*

biopharmaceutics, vol. 16, no. 4, pp. 331-353, 1988.

[23] E. A. Mueller, J. M. Kovarik, J. B. van Bree, W. Tetzloff, J. Grevel and K. Kutz, "Improved dose linearity of cyclosporine pharmacokinetics from a microemulsion formulation," *Pharmaceutical research,* vol. 11, no. 2, pp. 301-304, 1994.

[24] K. Atkinson, J. C. Biggs, K. Britton, R. Short, R. Mrongovius, A. Concannon and A. Dodds, "Oral administration of cyclosporin A for recipients of allogeneic marrow transplants: implications of clinical gut dysfunction," *British journal of haematology,* vol. 56, no. 2, pp. 223-231, 1984.

[25] R. Venkataramanan, G. J. Burckhart and R. J. Ptachcinski, "Pharmacokinetics and monitoring of cyclosporine following orthotopic liver transplantation," *Seminars in liver disease,* vol. 5, no. 4, pp. 357-368, 1985.

[26] B. G. Ericzon, S. Todo, S. Lynch, I. Kam, R. J. Ptachcinski, G. J. Burckart, D. H. Van Thiel, T. E. Starzl and R. Venkataramanan, "Role of bile and bile salts on cyclosporine absorption in dogs," *Transplantation proceedings,* vol. 19, no. 1, p. 1248, 1987.

[27] N. Honcharik, "The effect of food on cyclosporine absorption," *Clinical biochemistry,* vol. 24, no. 1, pp. 89-92, 1991.

[28] S. K. Gupta and L. Z. Benet, "Food increases the bioavailability of cyclosporine in healthy volunteers," *Clinical Pharmacology and Therapeutics,* vol. 45, no. 2, pp. 148-148, 1989.

[29] R. J. Ptachcinski, R. Venkataramanan, J. T. Rosenthal, G. J. Burckart, R. J. Taylor and T. R. Hakala, "The effect of food on cyclosporine absorption," *Transplantation,* vol. 40, no. 2, pp. 174-176, 1985.

[30] G. Wu, P. Cossettini and M. Furlanut, "Prediction of blood cyclosporine concentrations in haematological patients with multidrug resistance by one-, two-and three-compartment models using Bayesian and non-linear least squares methods," *Pharmacological research,* vol. 34, no. 1, pp. 47-57, 1996.

[31] F. Follath, S. Vozeh, G. Thiel, F. Brunner, R. Loertscher, M. Lemaire, K. Nussbaumer, W. Niederberger and A. Wood, "Intravenous cyclosporine kinetics in renal failure," *Clinical Pharmacology & Therapeutics,* vol. 34, no. 5, pp. 638-643, 1983.

[32] M. Lemaire and P. Tillement, "Role of lipoproteins and erythrocytes in the in vitro binding and distribution of cyclosporin A in the blood," *J. Pharm. Pharmacol.* , vol. 34, pp. 715-718, 1982.

[33] F. Akhlaghi and A. K. Trull, "Distribution of cycllosporin in Organ trasplant receipients," *Clinical Pharmacokinetics,* vol. 41, no. 9, pp. 615-, 2002.

[34] K. P. Harris, G. I. Russell, S. D. Parvin, P. S. Veitch and J. Walls, "Alterations in lipid and carbohydrate metabolism attributable to cyclosporin A in renal transplant recipients," *Br Med J (Clin Res Ed),* vol. 292, p. 16, 1986.

[35] B. Legg and M. Rowland, "Cyclosporin: measurement of fraction unbound in plasma," *Journal of Pharmacy and Pharmacology,* vol. 39, no. 8, pp. 599-603, 1987.

[36] J. Boland, K. Atkinson, K. Britton, P. Darveniza, S. Johnson and J. Biggs, "Tissue distribution and toxicity of cyclosporin A in the mouse," *Pathology,* vol. 16, no. 2, pp. 117-123, 1984.

[37] C. T. Ueda, M. Lemaire and P. Misslin, "Pharmacokinetic evaluation of the blood-to-lymph transfer of cyclosporin a in rats," *Biopharmaceutics & drug disposition,* vol. 4, no. 1, pp. 83-94,

1983.

[38] B. D. Kahan, C. T. Van Buren, M. Boileau, M. Ried, W. D. Payne, S. Flechner and J. Newburger, "Cyclosporin A tissue levels in a cadaver renal allograft recipient," *Transplantation,* vol. 35, no. 1, pp. 96-99, 1983.

[39] F. T. Aweeka, S. J. Tomlanovich, T. Prueksaritanont, S. K. Gupta and L. Z. Benet, "Pharmacokinetics of Orally and Intravenously Administered Cyclosporine in Pre-Kidney Transplant Patients," *The Journal of Clinical Pharmacology,* vol. 34, no. 1, pp. 60-67, 1994.

[40] G. C. Yee, T. P. Lennon, D. J. Gmur, M. S. Kennedy and H. J. Deeg, "Age-dependent cyclosporine: pharmacokinetics in marrow transplant recipients," *Clinical Pharmacology & Therapeutics,* vol. 40, no. 4, pp. 438-443, 1986.

[41] G. Maurer, H. R. Loosli, E. Schreier and B. Keller, "Disposition of cyclosporine in several animal species and man. I. Structural elucidation of its metabolites," *Drug Metabolism and Disposition,* vol. 12, no. 1, pp. 120-6, 1984.

[42] B. D. Kahan, " Individualization of cyclosporine therapy using pharmacokinetic and pharmacodynamic parameters," *Transplantation,* vol. 40, no. 5, pp. 457-476, 1985.

[43] H. I. Katz, "Potential drug interactions with cyclosporine," *International journal of dermatology,* vol. 36, no. s1, pp. 18-24, 1997.

[44] J. F. Tjia, W. I. R. and D. Back, "Cyclosporin metabolism by the gastrointestinal mucosa," *British journal of clinical pharmacology,* vol. 31, no. 3, pp. 344-346, 1991.

[45] U. Christians and K. F. Sewing, "Cyclosporin metabolism in transplant patients," *Pharmacology & therapeutics,* vol. 57, no. 2-3, pp. 291-345, 1993.

[46] T. Kronbach, V. Fischer and U. A. Meyer, "Cyclosporine metabolism in human liver: Identification of a cytochrome P-450III gene family as the major cyclosporine-metabolizing enzyme explains interactions of cyclosporine with other drugs," *Clinical Pharmacology & Therapeutics,* vol. 43, no. 6, pp. 630-635, 1988.

[47] J. H. Charuk, P. Y. Wong and R. A. Reithmeier, "Differential interaction of human renal P-glycoprotein with various metabolites and analogues of cyclosporin A," *American Journal of Physiology-Renal Physiology,* vol. 269, no. 1, pp. F31-F39, 1995.

[48] K. R. Copeland, R. W. Yatscoff and R. McKenna, "Immunosuppressive activity of cyclosporine metabolites compared and characterized by mass spectroscopy and nuclear magnetic resonance," *Clinical chemistry,* vol. 36, no. 2, pp. 225-229, 1990.

[49] R. Venkataramanan, T. E. Starzl, S. Yang, G. J. Burckart, R. J. Ptachcinski, B. W. Shaw, S. Iwatsuki, D. H. Van Thiel, A. Sanghvi and H. Seltman, "Biliary excretion of cyclosporine in liver transplant patients," *Transplantation proceedings,* vol. 17, no. 1, pp. 286-289, 1985.

[50] J. S. Bleck, H. J. Schlitt, U. Christians, C. Thiesemann, S. Strohmeyer, R. Schottmann, K. Kohlhaw, K. Wonigeit and K. F. Sewing, "Urinary excretion of ciclosporin and 17 of its metabolites in renal allograft recipients," *Pharmacolog,* vol. 39, no. 3, pp. 160-164, 1989.

[51] R. J. Ptachcinski, R. Venkataramanan, G. J. Burckart, J. A. Gray, D. H. Thiel, A. Sanghvi and J. T. Rosenthal, "Cyclosporine kinetics in healthy volunteers," *The Journal of Clinical Pharmacology,* vol. 27, no. 3, pp. 243-248, 1987.

[52] C. Y. Wu, L. Z. Benet, M. F. Hebert, S. K. Gupta, M. Rowland, D. Y. Gomez and V. J. Wacher, "Differentiation of absorption and first-pass gut and hepatic metabolism in humans: Studies with cyclosporine," *Clinical Pharmacology & Therapeutics,* vol. 58, no. 5, pp. 492-497, 1995.

[53] S. K. Gupta and L. Z. Benet, "High-fat meals increase the clearance of cyclosporine," *Pharmaceutical research,* vol. 7, no. 1, pp. 46-48, 1990.

[54] K. S. Lown, R. R. Mayo, A. B. Leichtman, H. L. Hsiao, D. K. Turgeon, P. Schmiedlin-Ren, M. B. Brown, W. Guo, S. J. Rossi, L. Z. Benet and P. B. Watkins, "Role of intestinal P-glycoprotein (mdr1) in interpatient variation in the oral bioavailability of cyclosporine," *Clinical Pharmacology & Therapeutics,* vol. 62, no. 3, pp. 248-260, Lown, K.S., Mayo, R.R., Leichtman, A.B., Hsiao, H.L., Turgeon, D.K., Schmiedlin-Ren, P., Brown, M.B., Guo, W., Rossi, S1997.

[55] C. W. Clardy, T. J. Schroeder, S. A. Myre, N. K. Wadhwa, A. J. Pesce, M. R. First, P. T. McEnery, W. F. Balistreri, R. E. Harris and D. B. Melvin, "Clinical variability of cyclosporine pharmacokinetics in adult and pediatric patients after renal, car," *renal, cardiac, hepatic, and bone-marrow transplants. Clinical chemistry,* vol. 34, no. 10, pp. 2012-21, 1988.

[56] J. M. Kovarik, E. A. Mueller, J. B. van Bree, S. S. Flückiger, H. Lange, B. Schmidt, W. H. Boesken, A. E. Lison and K. Kutz, "Cyclosporine pharmacokinetics and variability from a microemulsion formulation-a multicenter investigation in kidney transplant patients," *Transplantation,* vol. 6, no. 58, pp. 658-663, 1994.

[57] K. N. Utecht, J. J. Hiles and K. J, "Effects of Genetic Polymorphisms on the Pharmacokinetics of Calcineurin Inhibitors," *Am J Health Syst Pharm,* vol. 23, no. 2340-2348, p. 63, 2006.

[58] N. von Ahsen, M. Richter, C. Grupp, B. Ringe, M. Oellerich and V. W. Armstrong, "No influence of the MDR-1 C3435T polymorphism or a CYP3A4 promoter polymorphism (CYP3A4-V allele) on dose-adjusted cyclosporin A trough concentrations or rejection," *incidence in stable renal transplant recipients. Clinical Chemistry,* vol. 47, no. 6, pp. 1048-1052, 2002.

[59] D. A. Hesselink, R. H. Schaik, I. P. Heiden, M. Werf, P. J. Gregoor, J. Lindemans, W. Weimar and T. Gelder, "Genetic polymorphisms of the CYP3A4, CYP3A5, and MDR-1 genes and pharmacokinetics of the calcineurin inhibitors cyclosporine and tacrolim," *MDR-1 genes and pharmacokinetics of the calcineurin inhibitors cyclosporine and tacrolimus. Clinical Pharmacology & Therapeutics,* vol. 74, no. 3, pp. 245-254, 2003.

[60] S. Pollard, B. Nashan, A. Johnston, P. Hoyer, P. Belitsky, P. Keown and H. Helderman, "A pharmacokinetic and clinical review of the potential clinical impact of using different formulations of cyclosporin A," *Clinical therapeutics,* vol. 25, no. 6, pp. 1654-1669, 2003.

[61] A. Lindholm and B. D. Kahan, "Influence of cyclosporine pharmacokinetics, trough concentrations, and AUC monitoring on outcome after kidney transplantation," *Clinical pharmacology & Therapeutics,* vol. 42, no. 2, pp. 205-218, 1993.

[62] D. J. Taber, G. Baillie, E. E. Ashcraft, J. Rogers, A. Lin, F. Afzal, P. Baliga, P. R. Rajagopalan and K. Chavin, "Does bioequivalence between modified cyclosporine formulations translate into equal outcomes?," *Transplantation,* vol. 80, no. 11, pp. 1633-1635, 2005.

[63] M. E. Thompson, A. P. Shapiro, A. M. Johnsen, J. M. Itzkoff, R. L. Hardesty, B. P. Griffith, H. T. Bahnson, R. H. McDonald, A. Hastillo and M. Hess, "The contrasting effects of cyclosporin-A and azathioprine on arterial blood pressure and renal funfunction following cardiac

transplantation," *International journal of cardiology*, vol. 11, no. 2, pp. 219-229, 1986.

[64] L. C. Racusen and K. Solez, "Cyclosporin nephrotoxicity," in *International review of experimental pathology*, San Diego, CA, Academic Press, 1988, pp. 107-152.

[65] B. D. Myers, J. Ross, L. Newton, J. Luetscher and M. Perlroth, "Cyclosporine-associated chronic nephropathy," *New England Journal of Medicine*, vol. 311, no. 11, pp. 699-705, 1984.

[66] M. M. Meyer, M. Munar, J. Udeaja and W. Bennett, "Efficacy of area under the curve cyclosporine monitoring in renal transplantation," *Journal of the American Society of Nephrology*, vol. 4, no. 6, pp. 1306-1315, 1993.

[67] N. Issa, A. Kukla and H. N. Ibrahim, "Calcineurin inhibitor nephrotoxicity: a review and perspective of the evidence," *American journal of nephrology*, vol. 37, no. 6, pp. 602-612, 2013.

[68] M. Brunet, J. Campistol, O. Millan, E. Vidal, N. Esforzado, I. Rojo, O. Jimenez, F. Oppenheimer, J. Corbella and J. Martorell, "Pharmacokinetic and pharmacodynamic correlations of cyclosporine therapy in stable renal transplant patients: evaluation of long-term target C 2," *International immunopharmacology*, vol. 3, no. 7, pp. 987-999, 2003.

[69] M. Fukudo, I. Yano, S. Masuda, S. Fukatsu, T. Katsura, Y. Ogura, F. Oike, Y. Takada, K. Tanaka and K. Inui, "Pharmacodynamic analysis of tacrolimus and cyclosporine in living-donor liver transplant patients," *Clinical Pharmacology abd Therapeutics*, vol. 78, no. 2, pp. 168-181, 2005.

[70] C. M. Stein, J. J. Murray and A. J. Wood, "Inhibition of stimulated interleukin-2 production in whole blood: a practical measure of cyclosporine effect," *Clinical chemistry*, vol. 45, no. 9, pp. 1477-1484, 1999.

[71] C. M. Stein, A. J. Sadeque, J. J. Murray, C. Wandel, R. B. Kim and A. J. Wood, "Cyclosporine pharmacokinetics and pharmacodynamics in African American and white subjects," *Clinical pharmacology and therapeutics*, vol. 69, no. 5, pp. 317-323, 2001.

[72] E. Grześk, B. Malinowski, M. Wiciński, K. Szadujkis-Szadurska, T. A. Sinjab, S. Manysiak, B. Tejza, M. Słupski, G. Odrowąż-Sypniewska and G. Grześk, "Cyclosporine-A, but not tacrolimus significantly increases reactivity of vascular smooth mumuscle cells," *Pharmacological Reports*, vol. 68, no. 1, pp. 201-205, 2016.

[73] N. K. Wadhwa, T. J. Schroeder, A. J. Pesce, S. A. Myre, C. W. Clardy and M. R. First, "Cyclosporine drug interactions: a review," *Therapeutic drug monitoring*, vol. 9, no. 4, pp. 399-406, 1987.

[74] M. R. Weir, "Therapeutic benefits of calcium channel blockers in cyclosporine-treated organ transplant recipients: blood pressure control and immunosuppression," *The American journal of medicine*, vol. 90, no. 5, pp. s32-s36, 1991.

[75] C. L. Smith, E. M. Hampton, J. A. Pederson, L. R. Pennington and D. W. Bourne, "Clinical and Medicoeconomic Impact of the Cyclosporine-Diltiazem Interaction in Renal Transplant Recipients," *Pharmacotherapy. The Journal of Human Pharmacology and Drug Therapy*, vol. 14, no. 4, pp. 471-481, 1994.

[76] H. Carstensen, N. Jacobsen and H. Dieperink, "Interaction between cyclosporin A and phenobarbitone [letter]," *British journal of clinical pharmacology*, vol. 21, no. 5, pp. 550-551, 1986.

[77] G. F. Cooney, M. Mochon, B. Kaiser, S. P. Dunn and B. Goldsmith, "Effects of carbamazepine on cyclosporine metabolism in pediatric renal transplant recipients.," *Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy,* vol. 15, no. 3, pp. 353-356, 1995.

[78] D. Freeman, A. Laupacis, P. A. Keown, C. R. Stiller and S. G. Carruthers, "Evaluation of cyclosporin-phenytoin interaction with observations on cyclosporin metabolites," *British journal of clinical pharmacology,* vol. 18, no. 6, pp. 887-893, 1984.

[79] G. C. Yee and D. R. Salomon, "Cyclosporine," in *Applied pharmacokinetics: principles of therapeutic drug monitoring. 3rd ed.* , Baltimore (MD), Lippincott Williams & Wilkins, 1992, pp. 28:1-40.

[80] S. Bauer, E. Störmer, A. Johne, H. Krüger, K. Budde, H. H. Neumayer, I. Roots and I. Mai, "Alterations in cyclosporin A pharmacokinetics and metabolism during treatment with St John's wort in renal transplant patients," *British Journal of Clinical Pharmacology,* vol. 55, no. 2, pp. 203-211, 2003.

[81] M. P. Ducharme, L. H. Warbasse and D. J. Edwards, "1995. Disposition of intravenous and oral cyclosporine after administration with grapefruit juice," *Clinical pharmacology and therapeutics,* vol. 57, no. 5, pp. 485-491, 1995.

[82] G. J. Burckart, T. Starzl, L. Williams, A. Sanghvi, C. Gartner Jr, R. Venkataramanan, B. Zitelli, J. Malatack, A. Urbach, W. Diven and R. Ptachcinski, "Cyclosporine Monitoring and Pharmacokinetics in Pediatrie Liver Transplant Patients," *Transplantation proceedings,* vol. 17, no. 1, p. 1172, 1985.

[83] G. C. Yee, G. Mills, R. Schaffer, T. P. Lennon, M. S. Kennedy and H. J. Deeg, "Renal Cyclosporine Clearance in Marrow Transplant Recipients: Age-Related Variation," *The Journal of Clinical Pharmacology,* vol. 26, no. 8, pp. 658-661, 1986.

[84] D. I. Min, M. Lee, Y. M. Ku and M. Flanigan, "Gender-dependent racial difference in disposition of cyclosporine among healthy African American and white volunteers," *Clinical pharmacology and therapeutics,* vol. 68, no. 5, pp. 478-486, 2000.

[85] R. Ogawa, J. M. Stachnik and H. Echizen, "Clinical pharmacokinetics of drugs in patients with heart failure," *Clinical pharmacokinetics,* vol. 52, no. 3, pp. 169-185, 2013.

[86] G. J. Burckart, R. Venkataramanan, R. J. Ptachcinski, T. E. Starzl, B. P. Griffith, T. R. Hakala, J. T. Rosenthal, R. L. Hardesty, S. Iwatsuki, J. Brady and D. H. Van Thiel, "December. Cyclosporine pharmacokinetic profiles in liver, heart, and kidney transplant patients as determined by high-performance liquid chromatography.," *Transplantation proceedings,* vol. 18, no. 6, pp. 129-136, 1986.

[87] K. Han, V. C. Pillai and R. Venkataramanan, "Population pharmacokinetics of cyclosporine in transplant recipients.," *The AAPS journal,* vol. 15, no. 4, pp. 901-912, 2013.

[88] M. Guada, A. Beloqui, M. R. Kumar, V. Préat, M. del Carmen Dios-Viéitez and M. J. Blanco-Prieto, "Reformulating cyclosporine A (CsA): More than just a life cycle management strategy," *Journal of Controlled Release,* vol. 225, pp. 269-282, 2016.

[89] S. Hamdy, A. Haddadi, A. Shayeganpour, A. Alshamsan, H. M. Aliabadi and A. Lavasanifar, "The immunosuppressive activity of polymeric micellar formulation of cyclosporine A: in vitro and in

vivo studies," *The AAPS journal*, vol. 13, no. 2, pp. 159-168, 2011.

[90] H. M. Aliabadi, D. R. Brocks and A. Lavasanifar, "Polymeric micelles for the solubilization and delivery of cyclosporine A: pharmacokinetics and biodistribution," *Biomaterials*, vol. 26, no. 35, pp. 7251-7259, 2005.

[91] R. J. Ptachcinski, G. J. Burckart, J. T. Rosenthal, R. Venkataramanan, D. L. Howrie, R. J. Taylor, E. D. Avner, D. Ellis and T. Hakala, "Cyclosporine pharmacokinetics in children following cadaveric renal transplantation," *Transplant Proc*, vol. 18, no. 4, pp. 766-7, 1986.

[92] R. Venkataramanan, G. J. Burckart, R. J. Ptachcinski, A. Lee, R. L. Hardesty and B. P. Griffith, "Cyclosporine pharmacokinetics in heart transplant patients," *Transplant Proc*, vol. 18, no. 4, pp. 768-70, 1986.

[93] S. Robson, J. Neuberger, H. P. Keller, E. Abisch, W. Neiderberger, B. V. Graffenried and R. Williams, "Pharmacokinetic study of cyclosporin A (Sandimmun) in patients with primary biliary cirrhosis," *British journal of clinical pharmacology*, vol. 18, no. 4, pp. 627-631, 1984.

[94] G. J. Burckart, R. Venkataramanan, R. J. Ptachcinski, T. E. Starzl, J. C. Gartner, B. J. Zitelli, J. J. Malatack, B. W. Shaw, S. Iwatsuki and D. H. Thiel, "Cyclosporine absorption following orthotopic liver transplantation," *The Journal of Clinical Pharmacology*, vol. 26, no. 8, pp. 647-651, 1986.

[95] M. A. McMillan, "Clinical pharmacokinetics of cyclosporin," *Pharmacology & therapeutics*, vol. 42, no. 1, pp. 135-156, 1989.

[96] G. F. Cooney, K. Habucky and K. Hoppu, "Cyclosporin pharmacokinetics in paediatric transplant recipients," *Clinical pharmacokinetics*, vol. 32, no. 6, pp. 481-495, 1997.

[97] V. Rodighiero, "Effects of liver disease on pharmacokinetics," *Clinical pharmacokinetics*, vol. 37, no. 5, pp. 399-431, 1999.

[98] S. M. Flechner, M. E. Kolbeinsson, J. Tam and B. Lum, "The impact of body weight on cyclosporine pharmacokinetics in renal transplant recipients," *Transplantation*, vol. 47, no. 5, pp. 806-10, 1989.

[99] B. J. Browne, C. Op'T Holt and O. E. Emovon, "Diurnal cyclosporine dosing optimizes exposure and reduces the risk of acute rejection after kidney transplantation," *Clinical transplantation*, vol. 15, no. s6, pp. 51-54, 2001.

[100] D. C. Campana, R. M. B. I. Buggia and M. Molinaro, "Clinically Significant Drug Interactions with Cyclosporin An Update," *Clinical pharmacokinetics*, vol. 30, no. 2, pp. 141-179, 1996.