



Clinical Pharmacokinetics and Pharmacodynamics of Voclosporin

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Accepted: 21 March 2023 / Published online: 3 May 2023
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Abstract

Voclosporin is an approved option for the long-term treatment of lupus nephritis. We aimed to provide a narrative review of the pharmacokinetics and pharmacodynamics of voclosporin. In addition, we derived values for pharmacokinetic and pharmacodynamic parameters by graphical analysis of published diagrams. Compared with cyclosporin, low-dose voclosporin is associated with a lower nephrotoxicity risk and, compared to tacrolimus, with a lower diabetes risk. After repetitive dosing of 23.7 mg twice daily and at target trough concentrations of 10–20 ng/mL, the dominant or effect-indicative half-life is estimated at 7 hours. Compared with the pharmacodynamics of cyclosporin, the potency of voclosporin is stronger, with a lower concentration CE_{50} of 50 ng/mL already producing the half-maximum immunosuppressive effect. The Hill coefficient can be predicted to be low at $H = 1.3$, indicating a concentration-dependent effect on the immune system. The corresponding effect bisection time of 10 hours allows for dosing every 12 hours. Accordingly, the trough concentration will be above the threshold concentration that produces 5% of the maximum effect of 5.2 ng/mL for immunosuppression but below both the predicted threshold of 30 ng/mL for nephrotoxicity and the predicted threshold of 40 ng/mL for new-onset diabetes. The pharmacokinetic and pharmacodynamic properties suggest the use of low-dose voclosporin combined with mycophenolate and low-dose glucocorticoids for immunosuppressive maintenance therapy.

Key Points

The pharmacokinetics of voclosporin suggest twice-daily dosing.

The pharmacodynamics of voclosporin allow for a lower dose than that with cyclosporine.

Low-dose voclosporin may be associated with less nephrotoxicity than cyclosporin and with less diabetes than tacrolimus.

1 Introduction

After cyclosporine and tacrolimus, the third calcineurin inhibitor that has been approved for patient therapy is voclosporin. This novel agent has been synthesised by chemical modification of the functional group at the amino acid-1 position of cyclosporine [10]. Despite the similarity between the new and parent molecules regarding the main structure and mechanism of action as well as the pharmacokinetic behaviour, this chemical modification confers distinctive properties to voclosporin, implying strong therapeutic potential.

Voclosporin has been investigated for its therapeutic effectiveness in a variety of immunological disorders, including non-infectious uveitis, psoriasis and lupus nephritis, as well as after organ transplantation [2, 5, 22, 26]. Based on a positive benefit-risk profile (the AURORA study), voclosporin received US Food and Drug Administration approval in January 2021 and European Medicines Agency approval in September 2022 for the treatment of adult patients with a diagnosis of active class III, IV or V lupus nephritis.

In addition to the immunosuppressive effect on T cells, a molecular effect on glomerular epithelial cells has been

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presumed to stabilise podocin and synaptopodin [35]. This mechanism on podocytes adds to the immune-mediated anti-proteinuric effect like cyclosporin and tacrolimus. The putative molecular effect on proteinuria takes time, but the response persists for 3 years under voclosporin maintenance therapy [4].

Since the development of voclosporin, several studies have described its pharmacological characteristics. However, some aspects are still elusive. Our paper aims to discuss the pharmacokinetics and pharmacodynamics of voclosporin. We extracted published data emphasising the clinical aspects. Based on published diagrams, we also estimated unreported pharmacokinetic and pharmacodynamic parameter values by use of the graphical analysis method [12].

We searched PubMed for papers using the untagged term “voclosporin”. Additionally, papers without open access were provided by the pharmaceutical company upon request (Otsuka). We extracted publications with clinical results and those with pharmacokinetic and pharmacodynamic data. In all papers, we searched for supporting pictures or self-evident figures and graphs that could be exported by a screen shot or by scanning. Finally, we attempted to derive suggestions for the practical use of voclosporin.

2 Pharmacokinetics of Voclosporin

2.1 Dosing and Formulation

Voclosporin is marketed in the form of capsules for oral use (Lupkynis®; Otsuka). The most convincing clinical results have been seen with low-dose voclosporin twice-daily (bid) 23.7 mg (bid 0.35 mg/kg) in the treatment of lupus nephritis, especially nephrotic syndrome [30].

2.2 Absorption

The bioavailability of oral voclosporin decreases when taken with food, whereas under fasted conditions, the maximum concentration ($C_{\max}$) is twice as high and the area under the curve (AUC) is larger [20]. However, no value on the absolute bioavailability can be found in the voclosporin literature.

Initially, the voclosporin dose used was 4.5 mg/kg or 300 mg, comparable to the conventional cyclosporin dose of 300 mg [17]. Because the 1000-ng/mL $C_{\max}$ and the AUC for 300 mg of voclosporin are similar to the $C_{\max}$ and AUC with conventional 300 mg of cyclosporin, the bioavailability after an oral dose must be comparable. For conventional cyclosporin, the bioavailability has been reported to be 57%, while the value is higher at 74% with the new microemulsion [6]. The similarity to conventional cyclosporin therefore allows us to

predict an oral bioavailability of approximately $F = 50\%$ for voclosporin (Table 1).

2.3 Distribution, Metabolism and Elimination

Voclosporin is highly bound to plasma proteins with an estimated plasma binding percentage of 97%. Voclosporin also has a high affinity for red blood cells, with the concentration and temperature controlling the distribution between whole blood and plasma. Voclosporin is metabolised in the liver mainly by cytochrome P450 3A4. The fraction eliminated by the kidney is low, at 2.1% [13]. Nevertheless, a 1.5-fold increase in the AUC was seen in patients with an estimated glomerular filtration rate (eGFR) <30 mL/min [18].

The apparent clearance after an oral dose is 60 L/h and the apparent volume of distribution is 2154 L [13]. The $C_{\max}$ values rise in proportion to the dose, whereas the AUC increases in an overproportionate manner with higher dosing [20].

2.4 Pharmacokinetic Drug Interactions

Because of cytochrome P450 inhibition, voclosporin concentrations rise when co-administered with ketoconazole, and because of the P-glycoprotein interaction, voclosporin concentrations decrease when combined with rifampicin [19]. However, P-glycoprotein inhibition by voclosporin has been interpreted as a mechanism to re-establishing intracellular glucocorticoid action in refractory Th17.1 lymphocytes [23]. In contrast to cyclosporin, there is no interaction with mycophenolate, and like tacrolimus, voclosporin does not inhibit the biliary excretion and enterohepatic recirculation of mycophenolate-glucuronide [35].

2.5 Elimination Kinetics

In contrast to the exposure kinetics of voclosporin, which follow a first-order behaviour, the situation with its disposition kinetics and decline in plasma concentrations is more complex. Under the drug label of voclosporin, it was reported that the mean terminal half-life ($T_{1/2}$) is approximately 30 hours (https://www.accessdata.fda.gov/drugs_atfda_docs/label/2021/1/213716s000.lbl.pdf). However, this value is of less relevance for clinical purposes, as it does not reflect the elimination kinetics in the phase that contributes most to the AUC.

Following a $C_{\max}$ of 1000 ng/mL, the dominant $T_{1/2}$ can be obtained from the published Fig. 2 with $T_{1/2} = 5.4$ hours for both voclosporin and cyclosporin [17]. When concentrations fell below 50 ng/mL, however, voclosporin elimination became slower and compatible with a multi-compartment pattern; here, the terminal $T_{1/2}$ was as long as 30 hours [13].

Table 1 Pharmacokinetic parameters of voclosporin

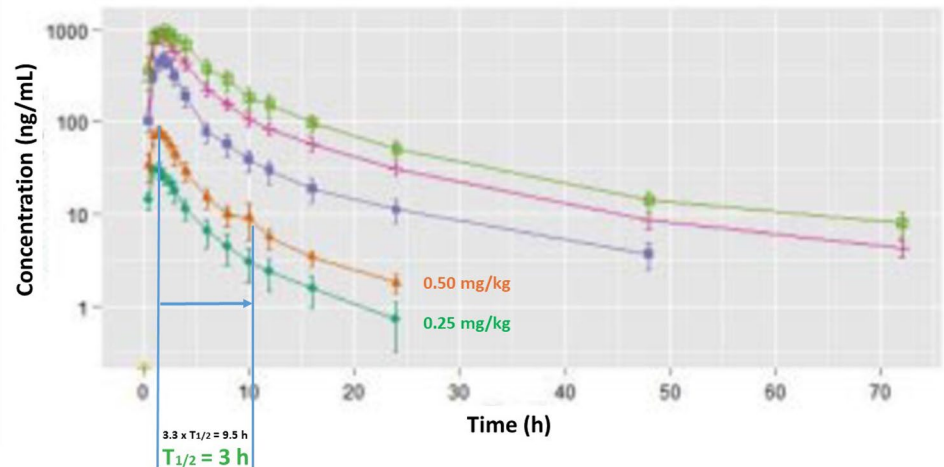
Dose	Parameter	Estimate	References
4.5 mg/kg	$C_{\max}$	1000 ng/mL	[17]
0.50 mg/kg		77 ng/mL	[20]
0.25 mg/kg		32 ng/mL	
0.35 mg/kg or 23.7 mg bid	C_{peak}	50–70 ng/mL	Here derived for the steady state
0.35 mg/kg or 23.7 mg bid	C_{trough}	10–20 ng/mL	
0.40 mg/kg bid		10–20 ng/mL	[5]
	Cl/F	60 L/h	[13]
	V_d/F	2154 L	
	$PB\%$	97%	
	f_{ren}	2.1%	
	F	50%	Here predicted bioavailable fraction
23.7 mg or 0.34 mg/kg	$T_{1/2}$	3.0 h	Interpolated from the values for 0.25 and 0.50 mg/kg in Fig. 3 from [17]
0.25 mg/kg		5.7 ± 2 h	[20]
		3.0 h	Graphical analysis Fig. 1 from [21]
0.50 mg/kg		3.0 h	Graphical analysis Fig. 1 from [21]
		7.0 h	Graphical analysis Fig. 2 from [17]
		7.9 ± 1.4 h	[20]
1.0 mg/kg		8.5 h	Estimated from population clearance and volume [17]
1.5 mg/kg		14.3 ± 2.9 h	[20]
4.5 mg/kg		18.1 ± 2.1 h	[20]
5.0 mg/kg		10 h	Graphical analysis from [17]
0.34 mg/kg or 23.7 mg bid	$T_{1/2 \text{ eff}}$	7.0 h	Predicted for the steady state
1.0 mg/kg multiple dose		34 h	Estimated from population clearance and volume [17]
	$T_{1/2 \text{ terminal}}$	30 h	[13]

bid twice daily, *Cl/F* apparent clearance, $C_{\max}$ maximum concentration, C_{peak} peak concentration, F bioavailable fraction after oral dose, f_{ren} fraction eliminated by the kidney, h hours, PB binding percentage, $T_{1/2}$ half-life, $T_{1/2 \text{ eff}}$ effect-indicative half-life, $T_{1/2 \text{ terminal}}$ terminal half-life, V_d/F apparent volume of distribution

In a study by Mayo and colleagues, it was also reported that voclosporin elimination becomes faster with decreasing doses [20]. With a high dose of voclosporin of 4.5 mg/kg,

the elimination declined with an elimination $T_{1/2}$ up to 18.1 ± 2.1 hours, while at 0.25 mg/kg, the elimination $T_{1/2}$ was reported to be less at 5.7 ± 2 hours [20]. From the published

Fig. 1 Dose-dependent concentration decline of voclosporin in a semi-logarithmic diagram. For the 0.50-mg/kg dose, concentrations fall from 100 to 10 ng/mL, and for the 0.25-mg/kg dose, they fall from 32 to 3.2 ng/mL [20]. The interval of one log level corresponds to 3.3 times one half-life. Accordingly, the elimination half-life can be predicted to be 3 hours for the standard 0.35-mg/kg dose (23.7 mg twice daily). h hours



graph, the $T_{1/2}$ can be derived as being as short as 3 hours for doses of 0.50 and 0.25 mg/kg (Fig. 1). Following peaks <100 ng/mL, however, no clear distinction can be made between the distribution and elimination kinetics.

In such complex situations, it is more informative to address the dominant $T_{1/2}$, which reflects the behaviour of the drug in the phase that represents most of the total AUC. From the Fig. 3 published elsewhere and by graphical analysis, the $T_{1/2}$ can be determined to be 3.0 hours for both doses of 0.25 and 0.50 mg/kg [17]. Thus, a single standard dose of 0.35 mg/kg or 23.7 mg will be eliminated with a short $T_{1/2}$ of 3.0 hours (Table 1).

Three explanations can be found for longer $T_{1/2}$ with higher doses (Fig. 2). First, the increase in $T_{1/2}$ might indicate a capacity-limited elimination, where the main route of elimination is by cytochrome P450 enzyme 3A4 metabolism. Such saturable Michaelis–Menten kinetics occur at higher concentrations, making elimination slower [15].

$$T_{1/2MM} \uparrow = 0.693 \cdot \frac{K_m + 0.75 \cdot C_{\max} \uparrow}{V_{\max}}$$

In addition, Michaelis–Menten-like metabolism could also be postulated to explain the partial autoinhibition of

liver enzymes by voclosporin after multiple dosing. After repetitive dosing of 23.7 mg with an administration interval of 12 hours (τ) for 10 days, the $T_{1/2}$ can be read off from Fig. 5 to increase from 3.0 to 7.0 hours [17]. Michaelis–Menten kinetics are capacity limited, and the maximum metabolism velocity ($V_{\max}$) can decrease after long-term administration.

$$T_{1/2MM} \uparrow = 0.693 \cdot \frac{K_m + 0.75 \cdot C_{\text{peak}}}{V_{\max} \downarrow}$$

When multiexponential kinetics become evident after multiple dosing, the accumulation factor (R_z) in a deep or slow compartment must also be taken into consideration. The accumulation factor (R_z) is higher for the concentration decline from the deep compartment ($R_z > R_a$), and the deep compartment half-life ($T_{1/2z}$) becomes dominant after multiple dosing.

$$R_z = \frac{1}{1 - \exp\left(-\frac{0.693}{T_{1/2z}} \cdot \tau\right)}$$

Thus, a combination of capacity-limited Michaelis–Menten kinetics with autoinhibition and deep-compartment

Fig. 2 Different patterns of concentration–time curves [15]. Michaelis–Menten kinetics are log-concave (red), biexponential kinetics are log-convex (green) and first-order kinetics are log-linear (blue)

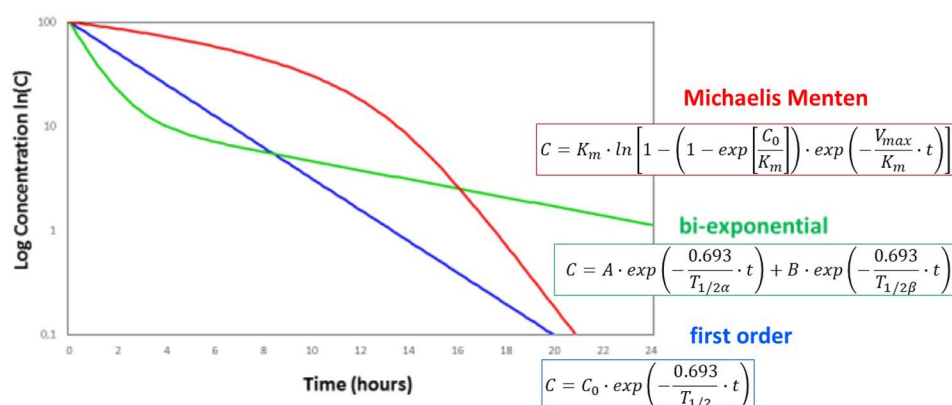
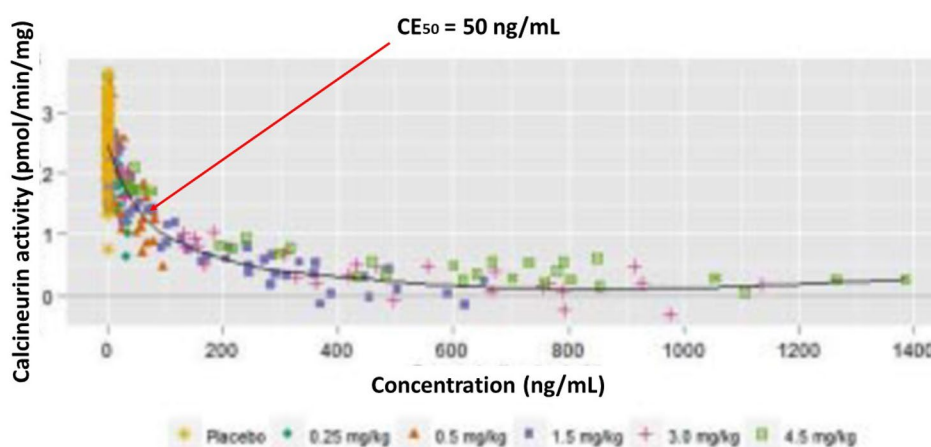


Fig. 3 Calcineurin activity depending on the voclosporin concentration [20]. By inhibition, the calcineurin activity decreases from 2.5 to 1.25 pmol/min/mg (or by 50%) at a voclosporin concentration of 50 ng/mL. CE_{50} concentration producing half-maximum inhibition



kinetics might be assumed for voclosporin after repetitive dosing. In addition, under both conditions, the clearance and the volume are not constant, as the drug clearance will decrease and the volume will increase when the $T_{1/2}$ increases after multiple dosing. Thus, on day 10 after repetitive dosing, a decrease in clearance from 1.0 to 0.3 L/h/kg and an estimate of the increase in volume from 12.3 to 14.7 L/kg have been reported [17]. Accordingly, after 10 days of dosing voclosporin 1.0 mg/kg with peaks at 100 ng/mL, an increase in the $T_{1/2}$ from 8.5 hours to even 34 hours can be estimated from published population clearance and volume parameters (Table 1). Therefore, all three parameters, namely, the $T_{1/2}$, volume and clearance, will change with multiple dosing.

$$T_{1/2} \uparrow \uparrow = 0.693 \cdot \frac{Vd/F \uparrow}{Cl/F \downarrow}.$$

For clinical purposes, the dominant or effect-indicative half-life ($T_{1/2 \text{ eff}}$) matters for determining multiple-dose kinetics. The $T_{1/2 \text{ eff}}$ parameter refers to the effect bisection time (TED_{50}) and the pharmacodynamic effect–concentration correlation (see Sect. 3.1.3); it is an extension of the “operational multiple dosing half-life” parameter [31]. The $T_{1/2 \text{ eff}}$ can be defined as the $T_{1/2}$ of the concentration decline between the target peak and target trough steady-state concentrations within one administration interval (τ).

$$T_{1/2 \text{ eff}} = \frac{\tau \cdot \ln(2)}{\ln(C_{\text{peak}}) - \ln(C_{\text{trough}})}.$$

After 6 months of voclosporin use at 0.40 mg/kg, low trough concentrations were measured between 10 and 20 ng/mL [5]. For a single dose of 0.50 mg/kg, the C_{max} is reported to be 77 ng/mL, but for a dose of 0.25 mg/kg, the C_{max} is 32 ng/mL [20]. For the recommended dose of 0.35 mg/kg (23.7 mg), the C_{max} can be interpolated as 50 ng/mL. Therefore, after repetitive administration of 23.7 mg bid, the range for target peak concentrations can be stated as being between 50 and 70 ng/mL, and for target trough concentrations, it is between 10 and 20 ng/mL. Accordingly, the $T_{1/2 \text{ eff}}$ will be estimated as being between 5.0 and 7.0 hours in the steady state. Otherwise, and because peaks are at least 50 ng/mL or higher after 23.7 mg, the reported $T_{1/2}$ of 30 hours would necessarily be associated with troughs of 40 ng/mL or higher.

3 Pharmacodynamics

3.1 Immunosuppressive Effect

Voclosporin, like other calcineurin inhibitors, exerts its action by blocking the activation of T-cell-specific

transcription factors such as the nuclear factor of activated T cells (NFAT). Several approaches have been proposed to measure the immunosuppressive effect of calcineurin inhibitors. In the case of cyclosporine and tacrolimus, a biomarker assay has been established to obtain a pharmacodynamic readout for their immunosuppressive effect [11]. This assay measures the combined change in the expression level of three NFAT-regulated genes, namely, interleukin-2, interferon- γ and granulocyte macrophage colony-stimulating factor, under the influence of these agents. The readout is a ratio between gene expression before and after drug intake and is termed “residual gene expression (RGE)”.

In contrast, the voclosporin pharmacodynamics have been characterised more upstream by direct measurements of phosphate ^{32}P radio-labelled calcineurin activity. Compared with cyclosporine, the suppression of calcineurin activity was determined to be similar but stronger and with less variability for voclosporin [2].

3.1.1 Hill Coefficient

Retrieving pharmacodynamic principles, it is important to recall that the effect (E) of a drug is a function of variable concentrations (C), of the specific concentration (CE_{50}) that produces half of the maximum effect (E_{max}), and of the Hill coefficient (H) that describes the sigmoidicity of the concentration–effect curve.

$$E = \frac{E_{\text{max}}}{1 + \left(\frac{CE_{50}}{C}\right)^H}.$$

Recall also that the higher the Hill coefficient is, the more sigmoidal the curve. For Hill coefficient values >2.0 , there is a “time-dependent” effect. It is not the peak concentration of the drug that is crucial for the effect, but rather, the exceeding of a critical threshold that matters, below which the effect is negligible. The longer the serum concentration of the drug is above this threshold, the greater is the expected effect.

However, for Hill coefficient values <2.0 , there is a “concentration-dependent” effect where the peak concentration matters. In such cases, an increasing effect can be achieved over a wide range by increasing the concentration. This categorisation of drugs according to the value of the Hill coefficient has been best described with antimicrobial drugs [8].

Applying the above Hill equation in the case of calcineurin inhibitors, the E_{max} corresponds to the maximum calcineurin or NFAT-RGE inhibition. The CE_{50} is the concentration producing half-maximum inhibition. Characterisation of the respective pharmacodynamic parameters

has been studied in healthy volunteers as well as in different patient cohorts for the different calcineurin inhibitors.

3.1.2 First-Generation Calcineurin Inhibitors

In healthy volunteers, the concentration producing 50% of maximum NFAT-RGE has been reported to be high at 204 ng/mL for cyclosporine and 15 ng/mL for tacrolimus [9]. The Hill coefficient was lower at $H = 1.86$ for cyclosporine and higher at $H = 2.13$ for tacrolimus.

We investigated NFAT-RGE in stable kidney transplant patients receiving triple therapy with tacrolimus, low-dose prednisolone and mycophenolate. Here, the concentration producing half-maximum NFAT-RGE inhibition (CE_{50}) was estimated to be low at 6.7 ng/mL, and the Hill coefficient H was 1.50, indicating concentration-dependent pharmacodynamics for tacrolimus [14]. Compared with volunteers, the higher sensitivity and the higher potency in kidney transplant patients are indicated by the lower CE_{50} , allowing for a lower dosage, most likely due to prednisolone also influencing NFAT-RGE [9].

3.1.3 Voclosporin

The pharmacodynamic properties of voclosporin after a single oral ascending dose in healthy human subjects have been previously studied by Mayo and colleagues, where the CE_{50} was determined to be 78 ng/mL [20]. In this study, however, the Hill coefficient as well as the exact half-life were not specified for the clinically used standard dose of voclosporin (0.34 mg/kg or 23.7 mg bid).

In the Hill equation, the concentration C is the pharmacokinetic variable and the concentration CE_{50} is the pharmacodynamic parameter. When the pharmacokinetic variable is equal to the pharmacodynamic parameter ($C = CE_{50}$), the $E_{\max}$ model can be used without knowing the Hill coefficient (H) because ($1.0^H = 1.0 = \text{const.}$). From the published

diagram [20], the voclosporin concentration producing the half-maximum calcineurin inhibition can be found to be 50 ng/mL (Fig. 3).

In addition, the trajectory of calcineurin inhibition allows us to graphically determine the time of effect duration. The TED_{50} is the specific time of the effect duration that it takes until the deepest inhibition is resolved and is again restored to 50% of both the pre-dose inhibition and the maximum inhibition by the respective dose. The time of effect duration is dose dependent, meaning that the bisection time TED_{50} increases with higher concentrations [15]. This bisection time can be found to be 4.5 hours for the voclosporin dose of 0.50 mg/kg (Fig. 4).

The specific TED_{50} is needed to restore one-half of the deepest inhibition of calcineurin activity. Based on the published diagram and graphical analysis, the TED_{50} is determined to be 4.5 hours [20]. The TED_{50} depends on the elimination $T_{1/2}$, on the maximum concentration ($C_{\max}$), on the concentration at half-maximum inhibition (CE_{50}) and on the Hill coefficient (H) according to a complex function [15].

$$TED_{50} = T_{1/2} \cdot \frac{1.44}{H} \cdot \ln \left[2 + \left(\frac{C_{\max}}{CE_{50}} \right)^H \right].$$

By use of this equation and single-dose (0.50 mg/kg) parameter values for $T_{1/2} = 3.0$ hours, $C_{\max} = 77$ ng/mL, $CE_{50} = 50$ ng/mL and $TED_{50} = 4.5$ hours, the Hill coefficient can be estimated for voclosporin by numerical iteration (Table 2). Thus, the Hill coefficient can be determined at $H = 1.30$ when the TED_{50} and CE_{50} values are inferred from published diagrams. In turn, these values allow us to estimate TED_{50} as 10 hours for the steady-state half-life of 7 hours (Table 2).

The abovementioned low Hill coefficient ($H = 1.30$) suggests that voclosporin action should be considered concentration dependent and that the target peak concentration should not be less than the concentration producing the

Fig. 4 Dose-dependent inhibition of calcineurin activity [20]. After the dose of 0.50 mg/kg, the activity decreased from 2.5 to 1.2 pmol/min/mg. To resolve the calcineurin inhibition and increase activity again to 1.9 pmol/min/mg, which is 50%, it takes 4.5 hours (TED_{50}). h hours

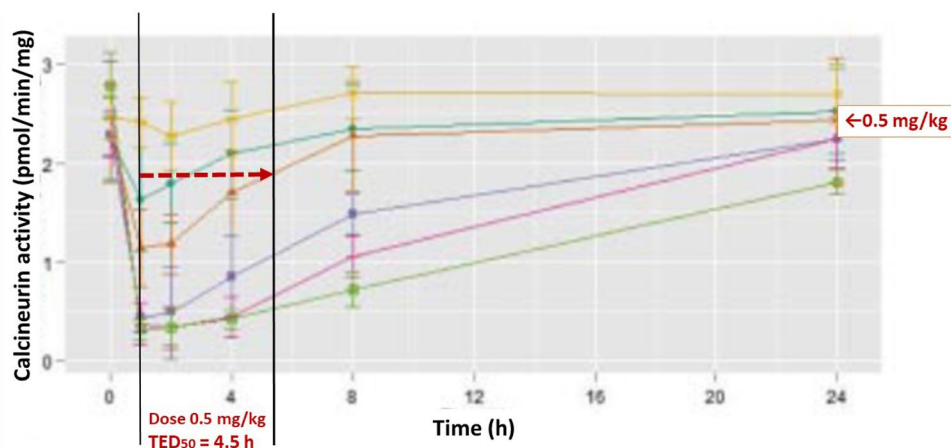


Table 2 Pharmacodynamic parameters (CE_{05} , CE_{50} and H) for beneficial voclosporin action on immunosuppression by calcineurin inhibition and for adverse effects such as nephrotoxicity or new-onset diabetes

Effect	Parameter	Estimate	Reference
Immunosuppression by calcineurin inhibition or NFAT-regulated gene expression	CE_{05}	5.0 ng/mL	Here derived
		20 ng/mL	Estimated from [21]
	CE_{50}	33 ng/mL	From diagram [5]
		50 ng/mL	Graphical analysis of Fig. 3 from [20]
		78.3 ± 6.8 ng/mL	[20]
		123 ± 12 ng/mL	[21]
	CE_{95}	482 ng/mL	Here derived
	TED_{50}	4.5 hours	Graphical analysis of Fig. 4 from [20]
	Hill coefficient (H)	1.30	Here derived
Nephrotoxicity		1.62	[21]
	TED_{50}	10 hours	Here derived for the steady-state $T_{1/2}$ of 7 h
	CE_{05}	30 ng/mL	From [5]
	CE_{50}	134 ng/mL	Here derived
	CE_{95}	600 ng/mL	Inferred from [2]
New-onset diabetes	Hill coefficient (H)	2.0	Here derived
	CE_{05}	40 ng/mL	Figure 5 as derived from [5]
	CE_{50}	70 ng/mL	Here derived
	CE_{95}	123 ng/mL	
	Hill coefficient (H)	5.2	

CE_{05} concentration that produces 5% of the maximum effect, CE_{50} concentration that produces half of the maximum effect, CE_{95} concentration that produces almost 95% of the maximum effect, $NFAT$ nuclear factor of activated T cells, TED_{50} effect bisection time

half-maximum effect ($C_{peak} \approx CE_{50}$). The predicted peak C_{peak} of 50–70 ng/mL after the established standard dose of 23.7 mg bid exactly fits this postulate.

The Hill coefficient $H = 1.30$ also allows us to derive the threshold concentration CE_{05} , where only 5% of the maximum effect will be obtained [15].

$$CE_{05} = CE_{50} \cdot 19^{\frac{-1}{H}}.$$

For voclosporin, the threshold can be estimated as $CE_{05} = 5.2$ ng/mL, below which the effect is negligible and less than 5% of maximum immunosuppression. The steady-state voclosporin trough concentration at the end of the administration interval should not fall below this threshold ($C_{trough} > CE_{05}$) to guarantee calcineurin inhibition throughout the whole dose interval. In an early clinical trial on the use of voclosporin in new kidney transplant patients (PROMISE Study), a dose of 0.40 mg/kg led to troughs between 10 and 20 ng/mL at steady state after 180 days [5]. These troughs are well above the predicted threshold of 5.2 ng/mL.

Similarly, the ceiling concentration CE_{95} that produces almost 95% of the maximum effect can be estimated [15].

$$CE_{95} = CE_{50} \cdot 19^{\frac{1}{H}}.$$

This estimate is 482 ng/mL (Table 2). Concentrations above this ceiling value produce no more immunosuppression but likely more adverse drug effects.

In kidney transplant patients, Mayo and colleagues have previously characterised the multiple-dose steady-state pharmacokinetic and pharmacodynamic properties of voclosporin. The authors created a population-pharmacokinetic/pharmacodynamic model of voclosporin [21]. With voclosporin administration for 28 days, steady state can be assumed. After administration of the maintenance dose of 70 mg bid, the steady-state trough concentrations at 150 ng/mL increased two-fold to peak of 300 ng/mL at a time to maximum concentration of 2 hours [21]. This two-fold concentration increase was mirrored by decreasing calcineurin activity from 1.5 to 0.5 pmol/min/mg, corresponding to a 66% inhibition at 2 hours after the morning dose [21]. The CE_{50} has been reported to be 122 ng/mL, and the Hill coefficient was estimated at $H = 1.62$ [21]. The estimated CE_{50} value is higher (122 ng/mL vs 50 ng/mL), but the Hill coefficient ($H = 1.62$) corresponds to our inferred value ($H = 1.30$).

A linear correlation between the effect and the trough concentrations was reported in the PROMISE study. In the published diagram, the CE_{50} was relatively low, and the value was graphically derived as 33 ng/mL [5]. Our calculated value of $CE_{50} = 50$ ng/mL is higher than 33 ng/mL but less than the reported CE_{50} of 78 ng/mL in volunteers not

taking glucocorticoids [20]. In kidney transplant patients taking corticosteroids, the CE_{50} was even higher at 123 ng/mL [21]. This result contrasts with our intuition and with the experience with tacrolimus, where the potency is higher and the CE_{50} is lower with glucocorticoid comedication [9].

However, with a CE_{50} of 123 ng/mL and a Hill coefficient $H = 1.62$ [21], the derived threshold concentration would be high at $CE_{05} = 20$ ng/mL. This value would require a higher dose voclosporin of >0.40 mg/kg (30 mg bid or more) to achieve steady-state troughs above this immunosuppressive threshold value. The lower half-maximum CE_{50} value of 50 ng/mL and the lower threshold CE_{05} value of 5.2 ng/mL derived here therefore come closer to the now established clinical dosing practice of 23.7 mg bid with peaks of 50–70 ng/mL and troughs of 10–20 ng/mL.

Unfortunately, comparable pharmacodynamic parameters cannot yet be derived for the molecular effect of voclosporin on synaptopodin and podocin stabilisation in glomerular podocytes. However, the pharmacodynamics of the adverse effects of voclosporin on the kidneys and glycaemia can be predicted.

3.2 Adverse Effects

The side-effect profile of voclosporin is comparable to that of other calcineurin inhibitors, where decreased glomerular filtration rate, hypertension, diabetes and an increased risk of infections, for example urinary tract infections, are among the most commonly reported adverse events. Understanding the dynamics of nephrotoxicity and new-onset diabetes is of utmost clinical importance, especially for patients with lupus nephritis.

3.2.1 Nephrotoxicity

Compared with cyclosporin, nephrotoxicity was reportedly less severe in a phase III trial on voclosporin [7]. A favourable risk-benefit ratio has been postulated for low-dose voclosporin 23.7 mg twice daily. In the 3-years follow-up, for example, the loss of glomerular filtration rate was less with voclosporin than in mycophenolate controls. With high-dose voclosporin (>0.80 mg/kg), however, adverse events were comparable to those with tacrolimus [5]. Now, we will provide a closer look at the dynamics of nephrotoxicity.

Previously, the pharmacodynamics of nephrotoxicity has been modelled for voclosporin. An AUC of 300 h·ng/mL was reported for a dose of 0.40 mg/kg [18]. Signs of nephrotoxicity and a 15% rise in serum creatinine were observed with a more than ten-fold higher AUC of 3448 h·ng/mL, which corresponds to a high dose of 3.0 mg/kg [2]. With low (0.40-mg/kg) and high (3.0-mg/kg) doses, the corresponding peak concentrations were expected at 60 and 600 ng/mL, respectively.

An acute toxic effect on the kidneys must be assumed if serum creatinine rises 1.5-fold or eGFR declines by 35% within <3 months [27]. For chronic nephrotoxicity, no comparable definition has yet been agreed upon. With an eGFR decline that is faster than the normal age-dependent decline of 1.0 mL/min per year, nephrotoxicity must be suspected even though serum creatinine can remain unchanged. However, any continuous and steady rise in serum creatinine that corresponds to a faster eGFR decline might indicate chronic kidney injury and nephrotoxicity.

Only in 6% of patients with psoriasis, a decline in eGFR was observed after a voclosporin dose of 0.40 mg/kg [28]. This dose will lead to voclosporin trough concentrations of 10–20 ng/mL. With a voclosporin dose of 0.80 mg/kg, however, the trough concentrations were 31–40 ng/mL [5]. In contrast to the voclosporin dose of 0.40 mg/kg, the serum creatinine at 6 months was significantly elevated at 131 μ g/mL with the higher 0.80-mg/kg dose and was higher than the creatinine value of 120 μ g/mL with tacrolimus [5]. Thus, nephrotoxicity and a $>10\%$ rise in creatinine after 6 months must be expected with a voclosporin dose of 0.80 mg/kg (56 mg bid) and trough concentrations >30 ng/mL. Accordingly, a dose of 0.50 mg/kg or less should be recommended to protect kidney function. From the published data on the 0.80-mg/kg dose in kidney transplant patients [5], the threshold CE_{05} for nephrotoxicity is found to be 30 ng/mL.

However, a 15% rise in creatinine was observed with a high voclosporin dose of 3.0 mg/kg [2]. This dose might correspond to a peak concentration of 600 ng/mL. Complementary to the nephrotoxic threshold concentration CE_{05} , the ceiling concentration CE_{95} can also be defined as the concentration where 95% of the maximum nephrotoxic effect would be attained. A 15% increase in serum creatinine corresponds to a 6.6-mL/min decrease in the eGFR. If this occurs within 6 months, the probability is near 95% that such concentrations produce nephrotoxicity, and no higher voclosporin concentration should be allowed; otherwise, the risk of an adverse effect on kidney function is 100% and confirmed.

Thus, 600 ng/mL can be seen as the nephrotoxic ceiling concentration (CE_{95}). From the threshold and ceiling concentrations, the concentration at half-maximum effect can be derived as the geometric mean value (CE_{50}) without knowing the Hill coefficient [15].

$$CE_{50} = \sqrt{CE_{05} \cdot CE_{95}}.$$

Therefore, the voclosporin concentration can be obtained, producing 50% of a likely nephrotoxic effect with $CE_{50} = 134$ ng/mL, where the threshold CE_{05} is 30 ng/mL and the ceiling CE_{95} is 600 ng/mL. From these estimates, finally, the Hill coefficient can also be predicted

as $H = 2.0$, placing this side effect between concentration-dependent and time-dependent pharmacodynamics [15].

$$H = \frac{\ln(19)}{\ln(CE_{50}) - \ln(CE_{05})}$$

For cyclosporine, acute kidney toxicity has been demonstrated to be concentration dependent, whereas chronic nephrotoxicity also depends on other factors [25]. Similarly, high peak concentrations should be avoided to prevent voclosporin injury to kidney function. This suggests a low maintenance dose and avoiding prolonging the administration interval to more than 12 hours.

3.2.2 New-Onset Diabetes

As an adverse event, new-onset diabetes after kidney transplantation (NODAT) has a prevalence of up to 25% in tacrolimus-treated cases [24]. Additionally, for voclosporin, the 6-month incidence of NODAT has been studied [5] and graphically depicted (Fig. 5). Because of concomitant glucocorticoids and in contrast to the published data, the NODAT incidence should start with a baseline risk, but it should not be at less than a zero-incidence value with a zero voclosporin concentration. Therefore, not the dotted line in Fig. 5 but a more sigmoidal correlation between NODAT and voclosporin concentrations must be assumed to underlie the determined values in the published diagram (red line, Fig. 5).

From the more sigmoidal correlation in the published diagram, a higher threshold concentration CE_{05} of 40 ng/mL might visually be derived (Fig. 5). Above this threshold,

the diabetes risk increases. This means that the voclosporin trough concentration should be less than 40 ng/mL to avoid new-onset diabetes.

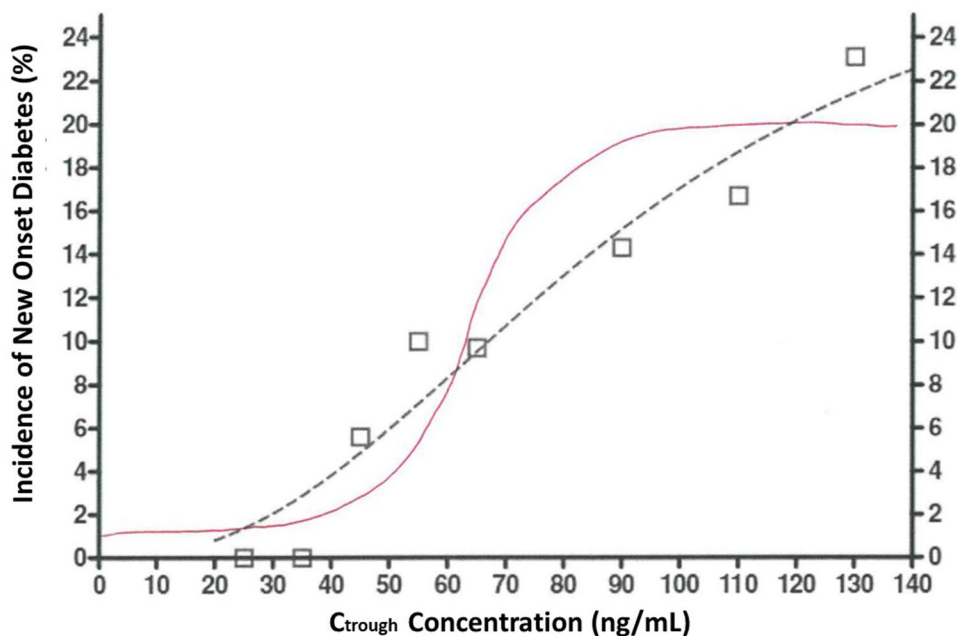
Based on a more sigmoidal correlation between the incidence of NODAT and voclosporin concentrations, the concentration producing the half-maximum risk of NODAT, the CE_{50} parameter, can be visually identified here at 70 ng/mL (Fig. 5). With a threshold CE_{05} of 40 ng/mL and a CE_{50} of 70 ng/mL, again, the Hill coefficient can be estimated by the above equation, and a relatively high estimate of $H = 5.2$ will result.

The high Hill coefficient of 5.2 indicates an over-proportional increase in the NODAT incidence with voclosporin trough concentrations higher than 40 ng/mL corresponding to a voclosporin dose of 0.80 mg/kg and higher. The diabetes risk, again, could be seen as an argument for selecting a low voclosporin dose of 0.50 mg/kg or less. Because voclosporin was combined with prednisolone and mycophenolate, the experience with kidney transplant patients can also be transferred to the diabetes risk in patients with lupus co-medicated with prednisolone and mycophenolate.

4 Pharmacogenetics

Pharmacogenetics have been investigated with the calcineurin inhibitors cyclosporin and tacrolimus. The homozygous TT and heterozygous T/C alleles of the cytochrome P450 3A5*3 polymorphism were found to be associated with increased clearance, low trough concentrations and insufficient immunosuppression for tacrolimus [1]. However, genotyping for the cytochrome P450 3A5 polymorphism

Fig. 5 Correlation between new-onset diabetes and voclosporin concentrations [5]. The red line corresponds to a more sigmoidal type of the effect-concentration correlation. C_{trough} trough concentration



did not result in better target concentration attainment than standard therapeutic drug concentration monitoring for tacrolimus [33].

Comparable observations on genetics have not been published for voclosporin. However, from the tacrolimus experience, further advantages of genotyping are not likely expected with voclosporin.

5 Conclusions and Practical Consequences

Because of the structural similarity between both drugs, the pharmacokinetics of voclosporin are comparable to those of cyclosporine. However, voclosporin is more potent than cyclosporine. Voclosporin shows some non-linearity in its pharmacokinetic disposition over the therapeutic range. Such differences imply a dose-dependent modification of the risk profile of voclosporin and lead to differential clinical applications, such as a low-dose regime.

The Hill coefficient of $H = 1.30$ can be seen as an argument for the prediction that voclosporin immunosuppression is concentration dependent, not time dependent. This means that a dose interval of 12 hours can be justified, although with multiple doses of 23.7 mg bid, the $T_{1/2\text{ eff}}$ is only between 5 and 7 hours. The corresponding TED_{50} of 7.3–10 hours also supports bid dosing.

The experience with cyclosporin might also allow predicting for voclosporin that elevated voclosporin concentrations will have an unfavourable effect on glomerular filtration rate. To avoid kidney dysfunction, the concentration range of voclosporin dosing should target values between 5.0 and 50 ng/mL, which are the threshold concentration and the concentration at half-maximum immunosuppression, respectively. With the low 23.7-mg bid voclosporin dose, no nephrotoxicity was observed in the 3-year observation period [4].

With low-dose voclosporin (<0.80 mg/kg), less NODAT has been demonstrated than with tacrolimus in kidney allografted patients [5]. A much lower dose of voclosporin (0.20 mg/kg), however, was associated with a higher rejection rate of 11% compared with 6% with tacrolimus after kidney transplantation [17].

Voclosporin achieved a complete renal response rate of 43% in lupus trials [3]. Even as an induction therapy, the multitargeted treatment of lupus nephritis with voclosporin and mycophenolate proved equivalent to tacrolimus and mycophenolate [16]. For the most dramatic form of acute kidney disease, that is, rapidly progressive glomerulonephritis, protocols containing voclosporin still must be investigated and compared to the established regimes [32].

Declarations

Funding Open Access funding enabled and organized by Projekt DEAL.

Conflicts of Interest/Competing Interests Frieder Keller received a 1200 € honorarium for participating in a teaching seminar at Otsuka company. Emaad Abdel-Kahaar has no conflicts of interest that are directly relevant to the content of this article.

Ethics Approval Not applicable.

Consent to Participate Not applicable.

Consent for Publication Not applicable.

Availability of Data and Material The authors possess no more than the published and referenced data, and more documented material is not available.

Code Availability Not applicable.

Authors' Contributions The first author, EAK, contributed to the review of clinical studies and the report of pharmacogenetic data. The second author, FK, contributed to the interpretation of pharmacokinetic and pharmacodynamic data and the figures. Both authors contributed to the writing of the text.

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