

Voclosporin: a novel calcineurin inhibitor with no impact on mycophenolic acid levels in patients with SLE

Teun van Gelder¹, Robert B. Huizinga², Laura Lisk² and Neil Solomons²

¹Department of Clinical Pharmacy and Toxicology, Leiden University Medical Center, Leiden, The Netherlands and ²Aurinia Pharmaceuticals, Victoria, BC, Canada

Correspondence to: Robert B. Huizinga; E-mail: rhuinga@auriniapharma.com

ABSTRACT

Background. An open-label phase 1 study was conducted to evaluate the effect of voclosporin following dosing with mycophenolate mofetil (MMF) on blood levels of mycophenolic acid (MPA, the active moiety of MMF) and MPA glucuronide (MPAG, the pharmacologically inactive metabolite of MMF) in subjects with systemic lupus erythematosus (SLE) and to assess the safety and tolerability of the combination.

Methods. MMF was orally administered at a dose of 1 g twice a day for at least 28 days prior to the study and continued at the same dose throughout the study. Voclosporin was orally administered at a dose of 23.7 mg twice a day for 7 consecutive days (Days 1–7), starting on the evening of Day 1 and ending with the morning dose on Day 7. Dense pharmacokinetic blood samples were collected pre-dose in the morning and from 0.25 to 12 h after the morning doses. Analyses were derived by non-compartmental methods.

Results. In 24 patients, MPA exposure [maximum serum concentration (C_{max}) and area under the concentration curve from time 0 to 12 h (AUC_{0-12})] was similar in the presence and absence of voclosporin, with treatment ratios of 0.94 and 1.09, respectively [C_{max} 16.5 μ g/mL (Day 1) versus 15.8 (Day 7), AUC_{0-12} 39.1 μ g/h/mL (Day 1) versus 40.8 (Day 7)]. MPAG exposure showed a small increase in the presence of voclosporin (12% for C_{max} and 27% for AUC_{0-12}). Combination therapy was well tolerated.

Conclusions. There is no clinically meaningful interaction between voclosporin and MMF. As changes in exposure to MPA may affect efficacy and safety, these data confirm that voclosporin and MMF can be administered concomitantly without the need for dose adjustment.

Keywords: drug–drug interactions, mycophenolic acid, pharmacokinetics, systemic lupus erythematosus, voclosporin

ADDITIONAL CONTENT

An author video to accompany this article is available at: https://academic.oup.com/ndt/pages/author_videos.

INTRODUCTION

Lupus nephritis (LN) is a common and potentially devastating manifestation of systemic lupus erythematosus (SLE) that occurs in more than half of SLE patients [1, 2]. Mycophenolate mofetil (MMF) and low-dose cyclophosphamide are recommended as first-line options for initial treatment of SLE in combination with a tapered steroid regimen [3].

In 2016, Zhang *et al.* [2] suggested that the efficacy of the calcineurin inhibitors (CNIs) cyclosporine and tacrolimus in induction therapy for LN was comparable to that of cyclophosphamide and MMF, with better tolerability. Furthermore, treatment with CNIs had comparable efficacy to azathioprine in long-term maintenance treatment, with fewer adverse effects [2]. Cyclosporine and tacrolimus are not approved for the treatment of LN and their use in this indication is considered off-label [4].

Voclosporin is a novel CNI developed for the treatment of LN. Voclosporin is structurally similar to cyclosporine A (CsA) except for modification of a functional group on the amino acid 1 residue. This changes the binding of voclosporin to calcineurin, leading to a molecule with improved potency when compared with CsA. This modification also shifts metabolism away from amino acid 1, the major site of metabolism for CsA, thus altering the metabolic profile. The combination of increased potency and a change in metabolite profile for voclosporin has led to a more consistent pharmacokinetic (PK)–pharmacodynamic relationship, administration of lower doses and potentially improved tolerability compared with CsA [5].

The main goals of LN treatment are the preservation of renal function and the prevention of flares; however, <50% of patients achieve complete remission at 1 year with the current standard-of-care therapy [6, 7]. Complete renal response (remission) definitions vary but can be summarized as a reduction in proteinuria with or without an improvement in estimated glomerular filtration rate (eGFR) [8, 9]. Complete renal response is associated with a low nephritis flare risk, greatly improved renal survival and increased overall survival [10]. Phase 2 and phase 3 studies showed that the addition of voclosporin to MMF and low-dose steroids increased renal response by 26.0% [odds ratio (OR) 3.21, $P < 0.001$] and 18.0% (OR 2.65, $P < 0.0001$) at 1 year, respectively (phase 3 data from published abstract) [11, 12].

Due to structural similarities between voclosporin and CsA and the reported drug–drug interaction (DDI) between CsA and MMF [13, 14], it is important to ascertain whether there is an interaction between voclosporin and MMF. The active moiety of MMF, mycophenolic acid (MPA), is metabolized in the liver to the inactive metabolite MPA glucuronide (MPAG), excreted into bile by the multidrug resistance-associated protein 2 (MRP2) and then undergoes enterohepatic recirculation. Enterohepatic recirculation contributes ~40% to overall MPA exposure as MPAG is deconjugated back to MPA in the gut by deglucuronidase activity of bacteria [15]. Research has shown that with increasing CsA pre-dose concentrations there is an incremental inhibition of the enterohepatic recirculation, leading to progressively lower MPA exposure; this leads to reduced effectiveness of MMF [14, 16, 17]. The mechanism responsible for the interaction is CsA-mediated inhibition of the excretion of MPAG into bile by the MRP2 transporter protein [15]. In clinical studies, MMF treatment in combination with CsA leads to up to 40% lower MPA exposure than when MMF is administered alone or with tacrolimus or sirolimus [15, 18, 19].

It has not yet been directly assessed if a DDI exists between voclosporin and MMF in patients with SLE. The primary objective of this study was to investigate the effect of voclosporin on blood levels of MPA and MPAG following dosing with MMF when both are dosed to a steady state in subjects with SLE.

MATERIALS AND METHODS

This was a multicentre, open-label, phase 1 study to evaluate the effect of voclosporin on the blood levels of MMF in male and female subjects 18–65 years of age with stable SLE with or without LN. Subjects taking a stable dose of oral MMF of 2 g/day (1 g twice a day) for at least 28 days prior to screening were eligible. Subjects continued the same MMF dose throughout the study. Voclosporin was administered at an oral dose of 47.4 mg/day (23.7 mg twice a day) for 7 consecutive days (Days 1–7), starting on the evening of Day 1 and ending with the morning dose on Day 7. Subjects remained at the study site for the duration of the treatment period (Days 1–7) and were discharged from the site after the Day 7 evening MMF dose. Subjects returned on Day 35 (± 3 days) for follow-up evaluations.

The study was conducted in accordance with the principles of the Declaration of Helsinki, International Council for

Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use Good Clinical Practice (GCP) guidelines and applicable laws and regulations. Prior to initiation of the study, the protocol and the informed consent form were reviewed and approved by the Quorum Review institutional review board (now known as Advarra).

PK sampling

Samples for PK analysis of MPA and MPAG were collected on Day 1 and for MPA, MPAG and voclosporin on Day 7 at pre-defined intervals: pre-morning dose(s) and at 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 3, 4, 5, 6, 8, 10 and 12 h after the morning dose(s).

Bioanalytical methods

MPA and MPAG were extracted from plasma samples by protein precipitation and measured using liquid chromatography tandem mass spectrometry (LC-MS/MS). The MPA assay was valid for concentrations of 0.100–30.0 $\mu\text{g/mL}$ with a precision of $\leq 6.2\%$ and an accuracy of -1.7 to 3.0% . The MPAG assay was valid for concentrations of 0.100–30.0 $\mu\text{g/mL}$ with a precision of $\leq 5.0\%$ and an accuracy of -0.4 to 5.0% .

Voclosporin was extracted from whole blood samples by protein precipitation and measured using LC-MS/MS [20]. The assay was valid for concentrations of 1–1000 ng/mL with a precision of $\leq 4.8\%$ and an accuracy of -8.3 to 3.0% .

Data handling

Subjects were included in the PK analysis if they provided sufficient samples to enable primary PK profiles to be derived following dosing with MMF and MMF plus voclosporin. Any missing values were excluded from the PK analysis. No imputation of PK values was performed. Observations below the limit of quantification or with non-determinable values were omitted from the analysis at the discretion of the pharmacokineticist.

PK analysis

PK analyses were performed using the validated computer program Phoenix WinNonlin (version 6.3; Certara, Princeton, NJ, USA). Standard non-compartmental analyses [model type: plasma (200–202), dose type: extravascular] were performed to calculate the PK parameters of MPA, MPAG and voclosporin by nominal PK sampling time. The PK concentrations by nominal PK sampling time and derived PK parameters for MPA, MPAG and voclosporin were summarized using descriptive statistics.

PK parameters were derived from the individual concentration–time profiles of MPA, MPAG and voclosporin by non-compartmental methods. A linear mixed effects model was applied to log-transformed PK parameter data [maximum serum concentration (C_{max}) and area under the concentration curve from time 0 to 12 h (AUC_{0-12})] with day and subject as fixed effects. The least squares mean and intrasubject coefficients of variation were derived from the model. The geometric mean ratios and the 90% confidence intervals (CIs) of the PK parameters of MPA and MPAG following administration of MMF with

and without voclosporin were constructed through back-transformed results based on the model.

DDI

As no prior study has examined the impact of voclosporin on MPA PK in SLE patients, a conservative approach was taken and the results were evaluated against the default equivalence range of 0.80–1.25. The potential effect of voclosporin on the steady-state PK of MMF was assessed by comparing the geometric mean ratios and the 90% CIs of the PK parameters of MPA and MPAG with (test) and without (reference) co-

administration of voclosporin. For the determination of no interaction, the no effect boundaries of 0.80–1.25 were applied.

RESULTS

Subject demographics

Thirty-six subjects were screened and 25 subjects were enrolled into the study; 23 subjects completed the study. Twenty-four of the 25 subjects enrolled completed PK sampling on both Day 1 and Day 7 and were included in the statistical PK analysis. One subject was withdrawn from the study on Day 4 due to non-treatment-related adverse events (AEs) of decreased glomerular filtration rate and increased creatinine. The AEs from the withdrawn subject were reported based on results from clinical laboratory tests taken prior to Day 1 voclosporin dosing, the results of which were received on Day 4. One other subject withdrew consent prior to the follow-up visit but after completion of the study treatment (Days 1–7).

The demographics of the subjects enrolled in the study are shown in Table 1. The majority of subjects [23 of 25 (92.0%)] were female. Eight subjects (32.0%) had a history of LN. The majority of subjects [20 of 25 (80.0%)] reported their race as White; the remaining five subjects (20.0%) reported their race as Black/African American. The subjects who selected White race were of Cuban, Hispanic, Latino or Spanish ethnicity.

Effect of voclosporin on MPA PK

The mean concentration–time profiles of MPA in plasma were similar in the presence and absence of voclosporin (Figure 1). The trough concentration (C_{trough}) values on Day 7 were similar to the morning pre-dose concentrations, suggesting achievement of steady-state conditions in the presence of voclosporin. MPA exposure parameters were similar in the absence and presence of voclosporin [C_{max} 16.5 µg/mL (Day 1)

Table 1. Subject characteristics

Demographics	Values
Age (years)	
Mean (SD)	47.4 (12.1)
Median (minimum–maximum)	49.0 (26.0–65.0)
Sex, n (%)	
Female	23 (92.0)
Male	2 (8.0)
Ethnicity, n (%)	
Not of Hispanic, Latino/a or Spanish origin	5 (20.0)
Cuban	6 (24.0)
Hispanic, Latino/a or Spanish origin	14 (56.0)
Race, n (%)	
Black or African American	5 (20.0)
White	20 (80.0)
Weight (kg)	
Mean (SD)	73.4 (11.5)
Body mass index (kg/m ²)	
Mean (SD)	27.4 (3.6)
Time since SLE diagnosis (years)	
Mean (SD)	9.0 (7.4)
Median (minimum–maximum)	6.0 (1.0–29.0)

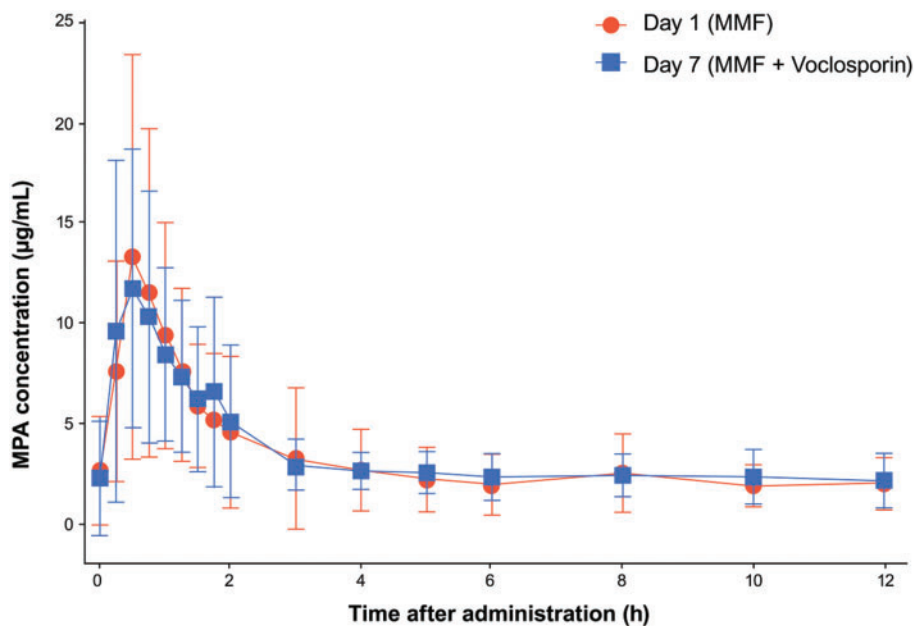


FIGURE 1: Mean (SD) plasma concentrations of MPA after administration of MMF alone (Day 1) and in the presence of voclosporin (Day 7).

versus 15.8 (Day 7), AUC_{0-12} 39.1 $\mu\text{g}/\text{h}/\text{mL}$ (Day 1) versus 40.8 (Day 7)]. The median time to maximum concentration (T_{max}) was similar on both days, with comparable ranges of individual values.

Based on the geometric mean ratios, MPA exposure was similar in the presence and absence of voclosporin. Observed intrasubject variability was high, as shown in Table 2.

Effect of voclosporin on MPAG PK

The mean concentration–time profiles of MPAG in plasma showed a small increase in the presence of voclosporin (Figure 2). C_{trough} values on Day 1 and Day 7 were similar to the morning pre-dose concentrations, suggesting achievement of steady-state conditions. MPAG exposure was higher following administration of MMF in the presence of voclosporin compared with administration of MMF alone [C_{max} 71.4 $\mu\text{g}/\text{mL}$ (Day 7) versus 65.0 (Day 1), AUC_{0-12} 532 $\mu\text{g}/\text{h}/\text{mL}$ (Day 7) versus 444 (Day 1)]. The median time to T_{max} was similar on both days, with comparable ranges of individual values.

Table 2. C_{max} and AUC_{0-12} of MPA after administration of MMF alone (Day 1) and in the presence of voclosporin (Day 7)

	MPA exposure ($n = 24$)	
	C_{max} ($\mu\text{g}/\text{mL}$)	AUC_{0-12} ($\mu\text{g}/\text{h}/\text{mL}$)
Geometric mean		
Day 1 (MMF)	14.8	36.2
Day 7 (MMF + voclosporin)	13.9	39.3
Geometric mean ratio (90% CI)	0.94 (0.77–1.16)	1.09 (0.94–1.26)
Intrasubject variability, % CV	43.8	29.9

CV, coefficient of variation.

Based on the geometric mean ratios, MPAG C_{max} and AUC_{0-12} were 12.0% and 27.0% higher, respectively, in the presence of voclosporin. The observed intrasubject variability was high with values of 27.7% and 34.4% for C_{max} and AUC_{0-12} , respectively.

Summary of safety

The safety population included all 25 subjects enrolled in the study. Administration of voclosporin with MMF over 7 days was well tolerated. Six subjects (24%) reported seven treatment-emergent AEs (i.e. an AE that started after the first dose of voclosporin), all of which were of mild or moderate intensity. There was one AE of tension headache considered to be treatment related and disease related. No subject was withdrawn from the study or had their study treatment discontinued as a result of a treatment-related AE. No deaths, severe AEs or serious AEs were reported during this study. No voclosporin treatment interruptions or dose modifications occurred and there were no clinically relevant changes in clinical laboratory parameters, vital signs, electrocardiograms and physical findings during the study. eGFR was assessed throughout the study and remained within normal limits. The mean eGFR was 92.5 ± 17.0 mL/min/1.73 m² at baseline, 89.3 ± 16.9 mL/min/1.73 m² at Day 7 and 93.4 ± 19.7 mL/min/1.73 m² at follow-up. There were no clinically significant changes observed in the SLE Disease Activity Index score between baseline and follow-up.

DISCUSSION

The principle PK findings of this study demonstrate that the administration of voclosporin with MMF does not affect exposure of MPA, the active moiety of MMF, and does not result in a clinically meaningful DDI. As changes in MPA may affect efficacy and safety, these data confirm that voclosporin and MMF

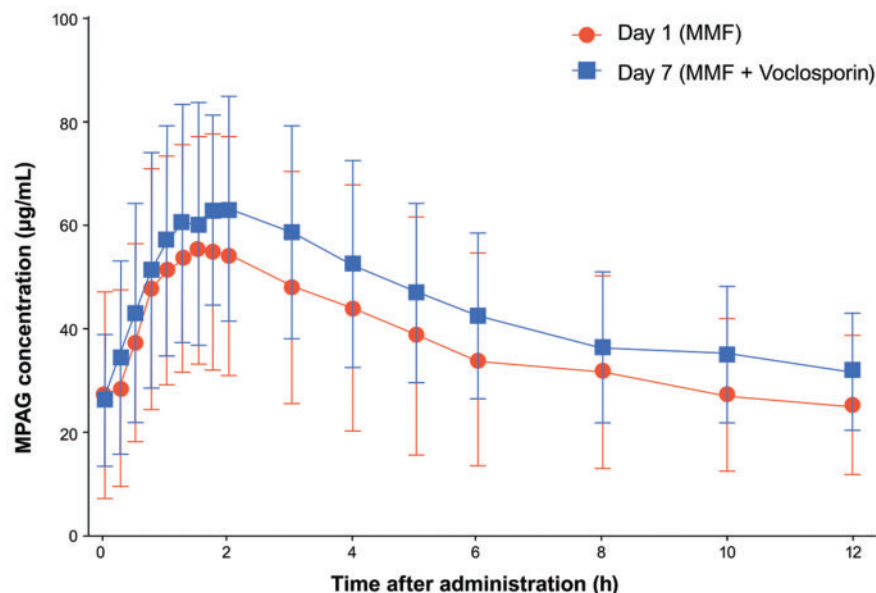


FIGURE 2: Mean (SD) plasma concentration of MPAG after administration of MMF alone (Day 1) and in the presence of voclosporin (Day 7).

can be administered concomitantly without the need to adjust the dose of MMF. The results from this study corroborate the PK analyses from a phase 2b renal transplantation study where exposure to MPA in MMF-treated patients did not differ among the voclosporin and tacrolimus treatment groups [21]. The observed intrasubject variability in MPA PK in the current study was high, consistent with previous reports [22].

An increase in MPAG exposure following administration with voclosporin was observed in this study. However, as MPAG is a pharmacologically inactive metabolite, this has no clinical relevance. Although MPAG is excreted by the kidney, the higher MPAG concentrations with voclosporin cannot be explained by changes in renal function, as renal function was stable (eGFR at study start and at Day 7 was 93.0 ± 17.0 and 89.0 ± 17.0 mL/min, respectively).

The study population, although limited in number, had representation from multiple ethnic groups and was indicative of the real-world population who may receive treatment for SLE [23]. The dose of MMF used in this study was in line with the treatment recommendations for LN [24].

Voclosporin administered in combination with MMF and low-dose steroids was well tolerated in phase 2 and 3 clinical studies of LN [11]. Consistent with these results, voclosporin and MMF were well tolerated over the 7 days of treatment in this study with no unexpected safety events.

CONCLUSION

Results from this DDI study give confidence to the addition of voclosporin to MMF and steroids in the treatment of LN. The results demonstrate a differentiated profile of voclosporin, compared with CsA, that may lead to more predictable immunomodulation when combined with MMF.

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DATA AVAILABILITY STATEMENT

The data underlying this article will be shared on reasonable request to the corresponding author.

AUTHORS' CONTRIBUTIONS

T.v.G., R.B.H., L.L. and N.S. designed the research, reviewed the analysis and wrote the manuscript. R.B.H., L.L. and N.S. performed the research.

CONFLICT OF INTEREST STATEMENT

T.v.G. has participated in studies supported by Chiesi, Aurinia Pharmaceuticals and Vitaeris. T.v.G. has participated in the Clinical Endpoints Committee of the AURA-LV and AURORA studies of Aurinia. He has also been on the speakers bureau of Astellas and has consulted for Roche Diagnostics. R.B.H., L.L. and N.S. are employees and stockholders of Aurinia Pharmaceuticals.

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