Selective Renal Tissue Disposition of the Calcineurin Inhibitors Voclosporin, Cyclosporine, and Tacrolimus

Simon Zhou[1], Krishani Kumari Rajanayake[2], Miao He[2], Bo Wen[2], Ankhbayar Lkhagva[2], Ernie Yap[1], Duxin Sun[2], Jennifer Cross[1], Kory Engelke[1], Robert B Huizinga[3]

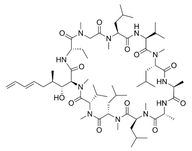
[1]Aurinia Pharmaceuticals Inc., Edmonton, AB, Canada, [2]University of Michigan College of Pharmacy, Ann Arbor, MI, United States, [3]Reformation Consulting Services, North Saanich, BC, Canada

BACKGROUND

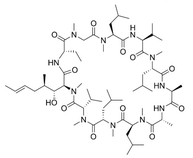
CALCINEURIN INHIBITORS

- The calcineurin inhibitors (CNIs) cyclosporine A (CSA) and tacrolimus (TAC) were revolutionary immunosuppressants when first introduced for solid organ transplantation in the 1980s[1]
- Voclosporin, a novel CNI, recently became the first oral therapy approved in the United States and Europe for the treatment of active lupus nephritis (LN) in adult patients based on positive results from Phase 2 and 3 clinical trials[2]
- Unlike CSA and TAC, voclosporin has a consistent pharmacokinetic and pharmacodynamic profile, eliminating the need for therapeutic drug monitoring. In clinical trials of LN, voclosporin was associated with a favorable lipid and glucose profile and no drug-drug interaction with mycophenolate mofetil (MMF)[2-6]
- Emerging evidence indicates small molecule therapeutics may display differential disposition within organ tissues; this suggests CNIs may be differentially distributed and retained in the kidney and may explain the difference in the efficacy and safety profiles of each CNI demonstrated in clinical trials[7-11]

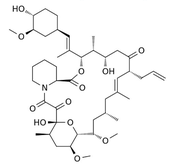
Voclosporin
$C_{63}H_{111}N_{11}O_{12}$
Molecular Weight: 1214.65 g/mol



Cyclosporine A
$C_{62}H_{111}N_{11}O_{12}$
Molecular Weight: 1202.64 g/mol



Tacrolimus
$C_{44}H_{69}NO_{12}$
Molecular Weight: 804.02 g/mol



STUDY OBJECTIVE

To evaluate the renal disposition of CSA, TAC, and voclosporin, we assessed in mice and humans the disposition of each CNI in the kidney relative to its systemic drug exposure

METHODS

Renal disposition in CD-1 mice

- Single, 30 mg/kg, doses of CSA, TAC, and voclosporin were administered intravenously to mice
- Kidneys were collected at different time points up to seven hours, flash frozen in liquid nitrogen, and stored at -20°C until sectioning
- Sections of 10 µm kidney tissue were mounted on indium tin oxide coated glass slides
- A matrix of 10 mg/mL α-Cyano-4-hydroxycinnamic acid in 85% acetonitrile/13% ethanol + 2% water + 0.1% trifluoroacetic acid was sprayed on the tissue using an HTX tissue sprayer, dried for 10 minutes in a vacuum, and subjected to matrix-assisted laser desorption and ionization mass spectrometry imaging (MALDI-MSI [atmospheric pressure (AP)-MALDI source coupled to Thermo Orbitrap ID-X])

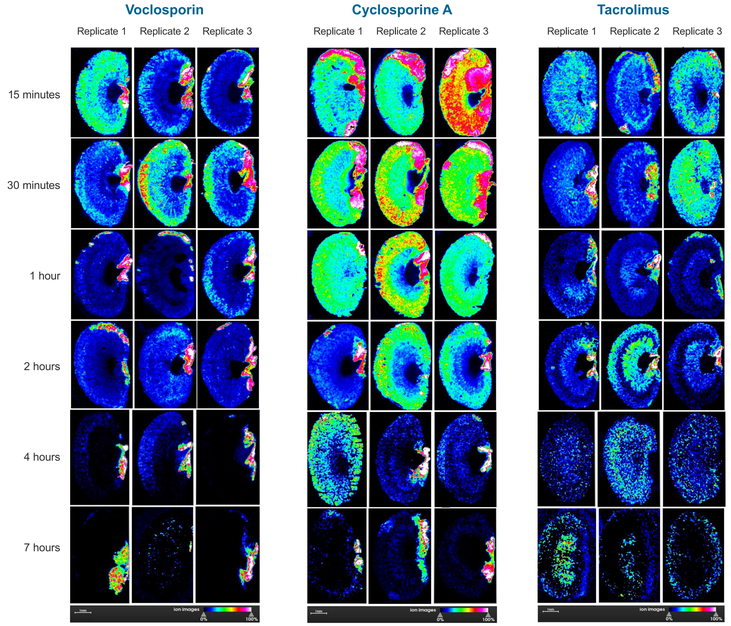
Renal disposition in humans

- Systemic clearance (CL), renal clearances (CLr), apparent clearance (CL/F), and fraction unbound (fu) of CSA and TAC in healthy human subjects were obtained from the literature[12-14]
- Pharmacokinetic data on voclosporin in humans was obtained from Aurinia Pharmaceuticals Inc.
- To assess the degree of renal secretion vs reabsorption of each CNI, the CLr of each drug was compared to its expected CL via passive filtration (glomerular filtration rate [GFR] x fu) and its respective systemic drug clearance

RESULTS

DIFFERENTIAL RENAL DISTRIBUTION AND RETENTION OF CNIs IN MICE

- MALDI-MSI demonstrated differential distribution and retention of voclosporin, CSA, and TAC in mouse kidneys
- Voclosporin had moderate distribution in the cortex and was rapidly excreted with low levels of drug present in the kidney after two hours
- Both CSA and TAC demonstrated more retention and diffuse distribution within the kidney than voclosporin, CSA to a greater degree than TAC
- TAC appeared to have prolonged drug retention in medulla up to 7 hr



- Moderate cortical distribution
- Minimal retention by 2 hours
- Diffuse distribution within kidney
- Cortico-medullary distribution and retention

Each panel represents the imaged kidney from a single animal, with three replicates imaged at each time point for each calcineurin inhibitor. Images collected via MALDI-MSI. The greater the concentration of drug present, the greater the intensity of color in the image, with blue indicative of low concentrations and white indicative of high concentrations.

DIFFERENTIAL RENAL REABSORPTION AND SECRETION OF CNIs IN HUMANS

- Voclosporin has a CLr of 7.82 mL/min representing approximately 200% of its expected passive filtration rate of 3.75 mL/min in humans[2,14,15]
- Based on the literature, CSA has a measured CLr of 1.48 mL/min in healthy humans, representing approximately 10% of the expected passive filtration of 12.5 mL/min[12]
- TAC has a CLr of 0.014 mL/min representing approximately 1% of the expected passive filtration of 1.25 mL/min[12]

	CL	CL/F	fu	Expected CLr (Passive filtration)	Actual CLr	Actual CLr/ Expected CLr
Voclosporin*	NA	1060 mL/min	3%	3.75 mL/min	7.82 mL/min	208.5%
Cyclosporine A	210-240 mL/min	NA	10%	12.5 mL/min	1.48 mL/min	11.8%
Tacrolimus	37.5 mL/min	NA	1%	1.25 mL/min	0.014 mL/min	1.1%

*Pharmacokinetic data for voclosporin specific to the orally-administered softgel formulation. Passive filtration = GFR x fu. Expected CLr > actual CL is suggestive of renal reabsorption. Expected CLr < actual CL is suggestive of renal secretion. CL, clearance; CLr, renal clearance; CL/F, apparent clearance; fu, fraction unbound in plasma; F, bioavailability; GFR, glomerular filtration rate; NA, not applicable.

CONCLUSIONS

- MALDI-MSI revealed differential retention and distribution of CSA, TAC, and voclosporin in mice, consistent with their respective renal clearances in humans
- Higher drug exposure in mouse kidney and >90% renal reabsorption based on the literature were reported for both CSA and TAC, whereas the renal handling of voclosporin suggested a significant component of tubular secretion
- The higher rate of secretion and lower overall exposure of kidney tissue to voclosporin may be associated with an improved safety profile when compared to the more diffuse distribution and greater renal retention of CSA and TAC
- Future research on the novel distribution and renal handling of voclosporin, cyclosporine A, and tacrolimus in humans will be illuminating in delineating the distinct clinical profiles of the CNIs

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WB, KKR, MH, BW, and AL have nothing to disclose.

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For more information, please contact Aurinia Medical Information at medinfo@auriniapharma.com.