A CALCINEURIN INHIBITOR WITH AN IMPROVED SIDE EFFECT PROFILE?

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INTRODUCTION AND AIMS

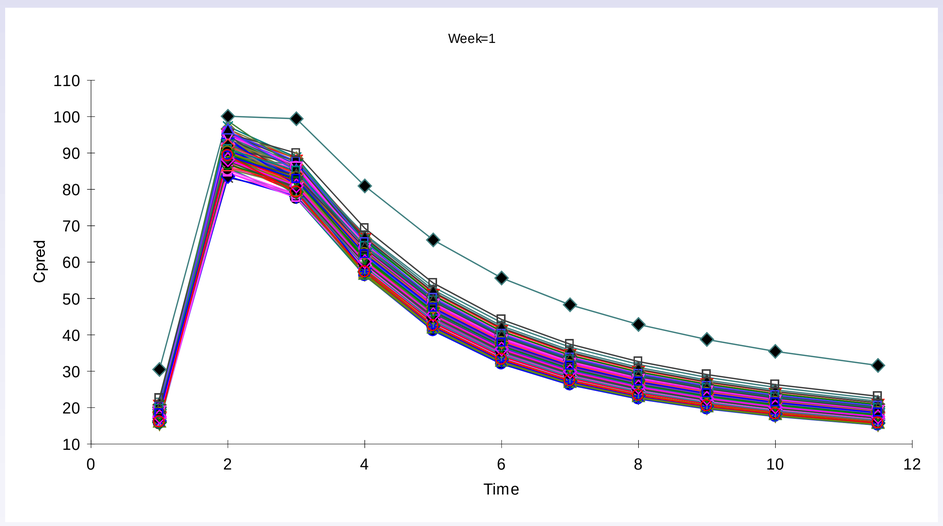
Voclosporin (VCS) is a novel calcineurin inhibitor (CNi) intended for use in the treatment of autoimmune diseases such as lupus nephritis. VCS was created by adding a single carbon extension to the amino acid-1 region of cyclosporine A. This alters the cyclophilin-voclosporin complex binding to calcineurin, increasing the potency of voclosporin and shifting the primary site for voclosporin metabolism resulting in less competitive antagonism. The results of these changes allows for the administration of lower doses, less pharmacokinetic-pharmacodynamic variability and a potentially improved safety profile compared with other CNIs. As Tacrolimus (TAC) and VCS inhibit calcineurin and prevent NFATc activation through different mechanisms, a Phase 2b renal transplant study (PROMISE) confirmed that the incidence of diabetes was significantly lower at 6 months post-transplant in a low-VCS treatment group compared to a TAC treatment group (1.6% vs. 16.4%, respectively, p = 0.031).

METHODS

To predict the adverse event profile of VCS in LN with fixed dosing, a population pharmacokinetic study was completed in renal allograft patients (n=274)[1], plaque psoriasis patients (n=341), renal/hepatic impaired patients (n=51)[2] and a pooled group of healthy patients participating in all Phase 1 studies (n=170)[3,4] treated with VCS. Patients dosed on a mg/kg BID dosing schedule had their fixed dose extracted and utilized for modeling purposes. Trough concentrations were compared with blood pressure and Modification of Diet in Renal Disease (MDRD) estimated glomerular filtration rate (eGFR) in plaque psoriasis patients.

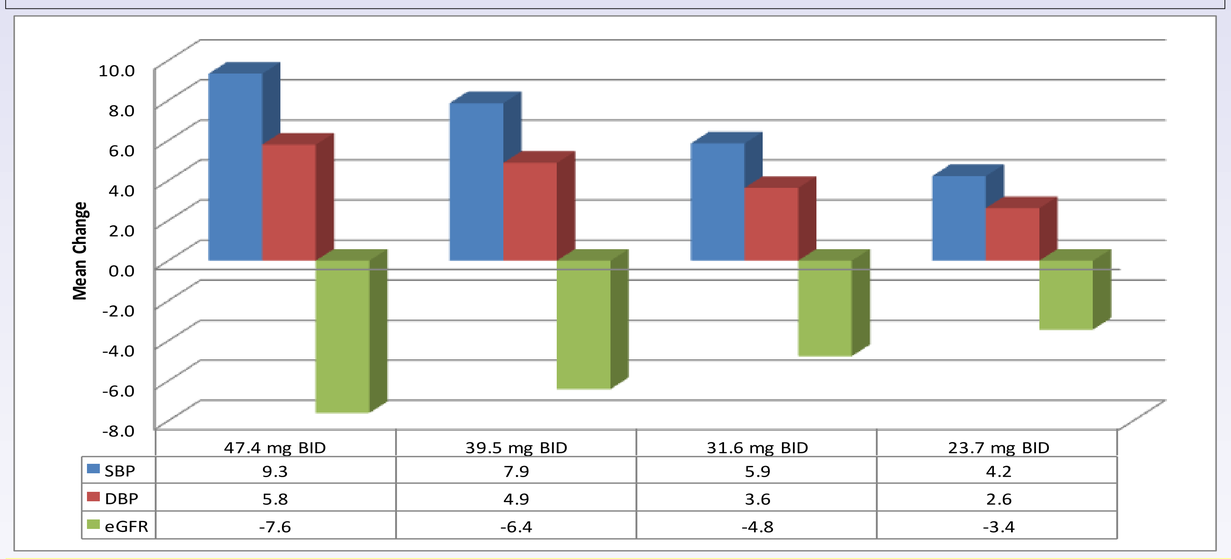
MODEL

Using a PopPK model, a theoretical lupus nephritis population was simulated. Using data from the Aspreva Lupus Management Studies[5,6] allowed for the simulation of lupus nephritis patients using the sample descriptive statistics for all covariates evaluated in the original full covariate model. Covariates were assumed to be normally distributed around their reported mean and standard deviation. A random sample was generated using R version 2.11.1. A voclosporin dose strategy was simulated which initiated therapy at 23.7 mg BID increasing 39.5 mg BID after two weeks. Week 1 simulated concentrations are shown below.



RESULTS

In this pooled population, as VCS trough concentrations increased a small change was observed in systolic and diastolic blood pressure with r^2 = 0.0622 and 0.061 respectively. Additionally, increasing drug concentrations resulted in a decrease in eGFR, with r^2 = 0.0448. To understand the impact in an ongoing global study in active LN (AURA-LV study) with fixed dosing concentrations of 23.7 and 39.5 mg BID, these data were then used to predict the mean change in BP and eGFR. Analysis revealed that the dose of 23.7 mg BID is predicted to produce a mean rise of 4.2 mmHg in systolic blood pressure, a 2.6 mmHg rise in diastolic blood pressure and a 3.4 mL/min decrease in eGFR.



	47.4 mg BID	39.5 mg BID	31.6 mg BID	23.7 mg BID
SBP	9.3	7.9	5.9	4.2
DBP	5.8	4.9	3.6	2.6
eGFR	-7.6	-6.4	-4.8	-3.4

CONCLUSIONS

Previously reported studies of VCS have demonstrated decreased incidence of diabetes compared to TAC. This predictive analysis in LN demonstrates the modest impact of VCS on systolic and/or diastolic blood pressure, with predicted effective immunosuppression. Given this data, a fixed dose regimen in LN without therapeutic drug monitoring may provide significant benefits in terms of ease of use. The AURA-LV study is ongoing in active lupus nephritis to validate this hypothesis.

ACKOWLEDGEMENTS AND REFERENCES

Thanks go to Drs. Patrick R. Mayo and Spencer Y. Ling who completed the analyses for Aurinia.

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