CALCINEURIN INHIBITION WITHOUT THERAPEUTIC DRUG MONITORING?

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INTRODUCTION AND AIMS

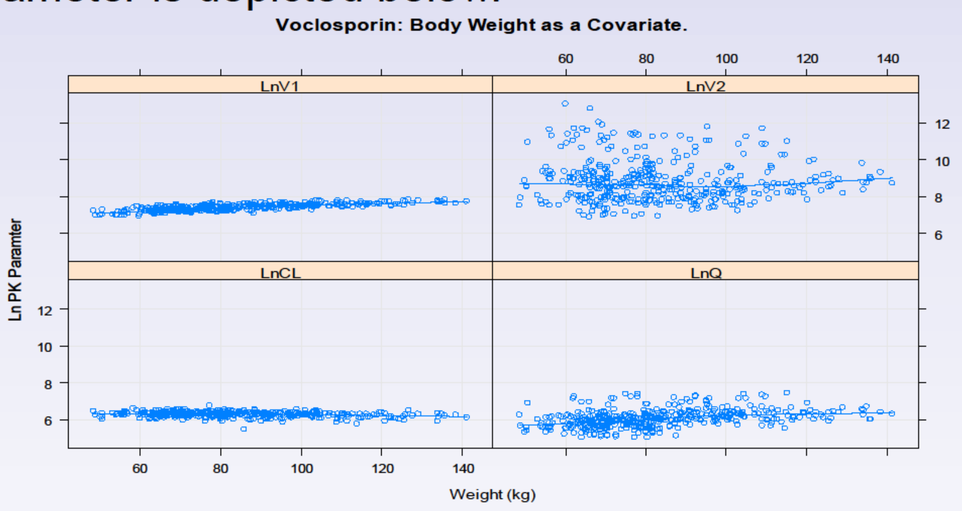
Voclosporin (VCS) is a novel CNI intended for use in the treatment of autoimmune diseases such as lupus nephritis (LN). VCS was created by adding a single carbon extension to the amino acid-1 region of cyclosporine A. X-Ray crystallography studies have shown that this addition alters cyclophilin-voclosporin complex binding to the catalytic and regulatory subunits in calcineurin. This change in binding has increased the potency of voclosporin relative to CsA and shifted the primary site for voclosporin metabolism to the amino acid-9 position. This leads to lower overall metabolite loads than seen for CsA resulting in less competitive antagonism with voclosporin. The combination of increased potency and a change in metabolite profile for voclosporin allows for administration of lower doses, less pharmacokinetic-pharmacodynamic variability and a potentially improved safety profile compared with other calcineurin inhibitors.

METHODS

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. A fully conditional Bayesian approach utilizing Markov Chain Monte Carlo (MCMC) with Gibbs sampling as implemented in PKBUGS(v1.1)/WinBugs(v1.4) was utilized. Two MCMC chains were run for a minimum of 10,000 iterations with the first 4000 iterations discarded. Covariates included age, weight, height, body surface area, sex, race, laboratory parameters and dosing day.

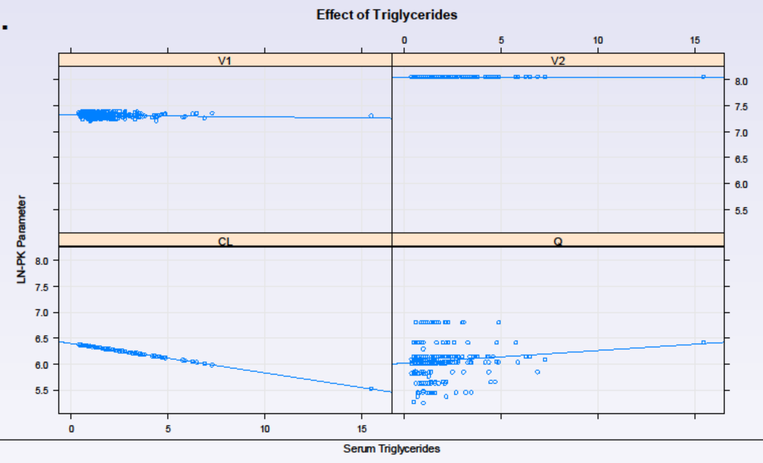
RESULTS 1

A 2-compartment extra-vascular model with absorptive lag provided a good fit for the multi-exponential pharmacokinetics observed for VCS. First compartment clearance and volume were denoted as CL and V1, while second compartment transfer and volume were denoted as Q and V2. WinBugs/PKBugs allows for testing of all pharmacokinetic parameters against the desired covariates. Importantly, subject body weight was not statistically credible for voclosporin clearance (CL and Q), or volume of distribution (V1 and V2). Subject body weight compared to the LN-pharmacokinetic parameter is depicted below.



RESULTS 2

Throughout model development trigylcerides and cholesterol appeared as significant covariates. It appears that serum triglycerides are important to the first-compartment clearance of the drug. Race and day also demonstrated an effect on second compartment clearance, with age having a minor yet credible effect on first compartment volume. The VCS molecule demonstrates significant lipophilicity partitioning rapidly into red blood cells often necessitating the presence of lipid compounds for solubility. Serum triglycerides demonstrate a reductive effect (0.945) on VCS first compartment clearance such that the higher the serum triglyceride concentration the lower the drugs oral clearance.



CONCLUSIONS

The most critical discovery of this analysis was a lack of effect by body weight on the pharmacokinetics of voclosporin. This clearly suggests that weight based dosing is not required to optimize the dosing of voclosporin. These data are important as other calcineurin inhibitors are impacted by patient weight. Thus, in LN a fixed dose regimen without therapeutic drug monitoring can be utilized which may provide significant benefits in terms of ease of use for both patients and physicians. The AURA-LV study is an ongoing global study of VCS in active LN with fixed dosing concentrations to validate this hypothesis.

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