Background Cytomegalovirus (CMV) infection is a major cause of morbidity in solid organ transplant recipients. Valganciclovir (ValG), prodrug of the antiviral ganciclovir, is used to prevent or treat CMV infection in this population. It is controversial in children. As the percentage of patients reaching the pharmacological target is too low with currently used ValG dosing regimen, our aim was to determine ganciclovir population pharmacokinetics in renal transplant children receiving ValG and propose an appropriate dosage regimen.

Methods After transplantation, children receiving ValG were monitored for plasma ganciclovir concentrations using high performance liquid chromatography. Population pharmacokinetics analysis was performed with NONMEM.

Results 1212 samples from 104 renal transplant patients, aged 2 to 20 years, received ValG to prevent (n=80), treat (n=12), or both prevent then treat (n=12) CMV infection. ValG was administered orally at a daily dose of 19.8 ± 10.1 mg/kg (mean ± SD). A two-compartment model with first-order elimination best fitted the data. At steady-state, AUClit = 64.5 ± 23.4 μg/mL-h, apparent clearance (CL/F) was 0.39 ± 0.14 L/h/kg, apparent volume of distribution at steady-state (VDss/F) was 2.4 ± 0.48 L/kg. Ganciclovir CL/F increased with body surface area (BSA) and was 15% higher in boys. Central volume of distribution increased with body surface area (BSA) and showed a 14% increase in boys. Internal validation was performed.

Conclusion We have successfully built a pharmacokinetic model allowing to propose dosages adapted individually to the characteristics of renal transplanted children.

Disclosure(s) Nothing to disclose

DEFINING SERUM CCL22 AND TREFOIL FACTOR 3 (TFF3) AS PHARMACODYNAMIC BIOMARKERS FOR USE IN A PROOF-OF-CONCEPT CLINICAL TRIAL OF VAMOROLONE IN PAEDIATRIC ULCERATIVE COLITIS

Background Paediatric ulcerative colitis (UC) patients would be well-served by a non-steroidal drug to control mucosal inflammation, without long-term and costly commitment to biologics. Vamorolone is a first-in-class alternative to glucocorticoids (GCs), under development for children with Duchenne muscular dystrophy (DMD); preliminary findings demonstrate improved safety compared with GCs seen in DMD patients treated with 6 mg/kg of vamorolone (47% vs. 33%). SOMAscan findings in UC validated by immunoassays. TFF3, measured by immunoassays, may be useful as objective biomarkers in UC. Serum CCL22 was correlated with change in Paediatric Ulcerative Colitis Activity Index (PUCAI) (p < 0.05 significance). Percent change in circulating CCL22 was compared with percent change in DMD patients treated with vamorolone (2 and 6 mg/kg/day, 2 weeks)2. Immunoassays were utilized to validate SOMAscan data.

Results CCL22 and TFF3 validated as decreased by GCs in IBD (p=0.005, p < 0.001). Decrease in TFF3 correlated with decrease in PUCAI (r=0.741, p=0.022); decrease in CCL22 did not correlate with change in PUCAI. Magnitude of CCL22 decrease in GC-treated UC patients was comparable to that seen in DMD patients treated with 6 mg/kg of vamorolone (47% vs. 33%). SOMAscan findings in UC validated by immunoassays.

Conclusion Decreases in serum CCL22 likely reflect effect on innate immune response, while decreases in serum TFF3 may reflect intestinal-specific effects of GCs in UC. CCL22 and TFF3, measured by immunoassays, may be useful as objective secondary outcomes reflective of NFkB inhibition and anti-inflammatory activity in a proof-of-concept trial of vamorolone in paediatric UC.

REFERENCES


Disclosure(s) LSC, JNvdA, and EPF are employees of Revere-Gen BioPharma. LSC and JNvdA own stock options of RevereGen. EPF is a co-founder of RevereGen and owns founder shares.

APPLICATION OF FETO-PLACENTAL-MATERNAL PHYSIOLOGICALLY-BASED PHARMACOKINETIC MODEL TO PREDICT TENOFOVIR CONCENTRATION DURING PREGNANCY

K Abduljalil, TN Johnson, M Jamel. Centara UK Limited, Simpeg Division, Sheffield, UK

Background Tenofovir is a drug used in combination with other anti-HIV drugs to treat patients with HIV-1 infection. It is used during pregnancy to reduce the risk of HIV transmission to the child. The aim of this work is to use a Physiologically-Based Pharmacokinetic (PBPK) model for prediction of maternal and fetal tenofovir concentration at birth.

Methods A full Feto-Placental-Maternal PBPK model that includes placenta as a 3-compartment permeability limited organ and 14 compartments for different fetal organs was developed using physiological1-2 and drug specific parameters3.
to predict tenofovir concentration in 50 virtual pregnant mothers at term after single administration of 600 mg of tenofovir disoproxil fumarate (272 mg tenofovir). The mechanistic model implemented using the Simcyp Lua interface within the Simcyp Simulator. Fetal as well as maternal tissue to plasma ratio values were predicted using the Rodgers & Rowland method with a scalar of 1.5. Predictions of tenofovir maternal and fetal plasma concentration were compared to reported observations.4

Results In spite of the large variability in the observed data, the model adequately replicated the maternal as well as fetal clinical observations.4 The placenta transfer by cotyledon was changed 10 times the mean reported value from perfusion experiment.4 All other model parameters were calculated using bottom-up approach. The maternal predicted-to-observed ratio for AUC24hr and Cmax was 1.13 and 1.08, respectively. The predicted fetal exposure was well predicted within the 5th and 95th percentiles and was 0.51 of maternal exposure (AUC24hr), the reported value is 0.60.4

Conclusion The developed feto-placental-maternal PBPK models can be used to predict drug exposure in fetal organs during in utero growth. The inter-subject variability can be predicted incorporating both the drug physicochemical properties and system (placental, maternal and fetal) parameters.

REFERENCES

Disclosure(s) Nothing to disclose

P03 GERMLINENUDT15 MUTATION AND THIOPURINES FOR CHILDREN WITH ACUTE LYMPHOBLASTIC LEUKEMIA: IS IT A PROGNOSTIC FACTOR?

1 M Simonin, 1A Petit, 2Y Mérard, 2A Benchikh, 2O Minikes, 1A Auvrignon, 1J Donadieu, 1G Leverger, 2E Jacqz-Aigrain, 2T Adam de Beaumais*. 1Trousseau Hospital; 2Robert Debré Hospital, Paris; 3Caen Hospital, Caen, France

Background The nudix hydrolase 15 (NUDT15) polymorphism recently emerges as a biomarker of severe hematological toxicity during 6-mercaptopurine (6-MP) therapy of children with acute lymphoblastic leukaemia (ALL). Initially described restricted to Asian population, recent publications highlighted its presence in patients with European ancestry. In November 2018, the Clinical Pharmacogenetics Implementation Consortium (CPIC) updated the guideline for thiopurines dosing based on Thiopurine S-methyl transferase (TPMT) and NUDT15 genotypes. Here, we presented a feedback from a French monocentric experience in ALL patients.

Methods We retrospectively genotyped 188 children for NUDT15 c.94C>A treated for ALL at Trousseau hospital, Paris. Parents have given their consent for thiopurines’ therapeutical drug monitoring including performing TPMT genotype (*2, *3B, *3C). We focused, for patients with a mutated NUDT15 genotype, on treatment response in terms of morbimortality.

Results This NUDT15 polymorphism was found for 6 patients (3.2%): one patient with a European ancestry and the others with an Asian ancestry. Five children had a NUDT15 mutated heterozygous genotype without TPMT alterations and one patient with a mutated homozygous NUDT15 genotype associated with TPMT *1/*3C. Hematological and/or infectious complications were reported for all patients with this variant with hospitalization in intensive care unit for the one with a mutated NUDT15 genotype and TPMT *1/*3C. Reduced 6-MP dose (between 30% to 50% of the standard dose for heterozygous patients and 3% of the standard dose for mutated homozygous patient) was required for maintenance therapy. Two patients had a relapse.

Conclusion This report supports CPIC guidelines for screening NUDT15 polymorphism before 6-MP treatment regardless patients’ race. The impact of this polymorphism on relapse occurrence is worrying and prospective results with dose adjustments at 6-MP initiation will be crucial to understand if...