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. 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 pharmacockinetics 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, $AUC_{24}h_{-ss}$ was 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, decreased with increasing creatinine concentration 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

O39 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

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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[1,2]. We sought to define NFkB-regulated, GC-responsive serum biomarkers for use in a proof-of-concept pilot trial of vamorolone in UC, focusing on TFF3 (produced by intestinal epithelia, GC-responsive in UC), and CCL22 (produced by macrophages, GC-responsive in UC and other inflammatory diseases)[3,4].
Methods Sera from 10 children with IBD (7 UC, 3 CD) were tested pre and post prednisone/prednisolone (1 mg/kg/day, max 40 mg, 1–4 weeks); 210 proteins responsive to GCs in UC [3] were analyzed using SOMAscan. Proteins that showed significant change over time were 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.

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Poster Presentations

P01 APPLICATION OF FETO-PLACENTAL-MATERNAL PHYSIOLOGICALLY-BASED PHARMACOKINETIC MODEL TO PREDICT TENOFOVIR CONCENTRATION DURING PREGNANCY

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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-comparment permeability limited organ and 14 compartments for different fetal organs was developed using physiological[1,2] and drug specific parameters[3]

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.[5] 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 (AUC24h), 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.

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P02 ALLOPURINOL COUNTERACTS INADEQUATE MERCAPTOPURINE METABOLISM IN PAEDIATRIC ACUTE LYMPHOBLASTIC LEUKEMIA

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Background Mercaptopurine (6-MP), a cornerstone of childhood acute lymphoblastic leukemia (ALL) therapy, is metabolized to active 6-thioguanine nucleotides (6-TGN) and 6-methylmercaptopurine nucleotides (6-MMPN) potentially hepatotoxic (threshold of 5000 pmol/8x10^8 RBC). In few cases, the equilibrium between 6-TGN and 6-MMPN is unbalanced and in favor to 6-MMPN with high risk of inefficacy and toxicities. Here, we treated patients with allopurinol which inhibits Xanthine Oxidase and Thiopurine S-methyl Transferase (*TPMT*) implicated in methylation of thiopurines.

Methods Therapeutic drug monitoring of ALL patients was based on the determination of metabolites concentrations in red blood cells, measured by HPLC-UV after 3 weeks of stable 6-MP dose. After parental consent, individual genotypes are determined for *TPMT* (*2, *3B, *3C), *ITPA* (c.94C>A) and *HLA*B5801* (prior to allopurinol) by TaqMan allelic discrimination.

Results In 8 patients, 6-MMPN/6-TGN ratio was too high, superior to 50 (range: 58–248) with 6-TGN under therapeutic threshold (< 250 pmol/8x10^8 RBC). All patients have a wild-type *TPMT* genotype and for 3 patients, *ITPA* polymorphism could be involved to this disequilibrium. The co-administration of Allopurinol (50 mg n=5, 100 mg n=2), with a reduced 6-MP dose (around -50%) dose had a positive impact on metabolic ratio, inferior to 15 (range: < 1- 13) with metabolites levels inside therapeutic window and on resolving some toxicities (hypoglycemia (n=4), hepatotoxicity (n=3)). For one patient, 200 mg of Allopurinol was administered without reducing 6-MP dose, the metabolic ratio decreased from 115 to 63 but metabolites levels were both at supratherapeutic levels.

Conclusion Allopurinol was effective in redirecting 6-MP metabolism to 6-TGN. A standardized protocol for this co-administration needs to be established and DNA-TGN incorporation dosage could be helpful for this recommendation. Long-term follow-up is required to evaluate impact on safety and efficacy of ALL maintenance therapy.

Disclosure(s) Nothing to disclose

P03 GERMLINE *NUDT15* MUTATION AND THIOPURINES FOR CHILDREN WITH ACUTE LYMPHOBLASTIC LEUKEMIA: IS IT A PROGNOSTIC FACTOR?

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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 leukemia (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' therapeutic drug monitoring including performing *TPMT* genotype (*2, *3B, *3C). We focused, for patients with a mutated *NUDT15* genotype, on treatment response in terms of morbi-mortality.

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