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 AUC_{24hr} and C_{max} 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 (AUC_{24h}), the reported value is 0.60.⁴

Conclusion The developed fetoplacental-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

1. Abduljalil, et al. *Clin Pharmacokinet* 2018;**57**(9):1149–1171.
2. Abduljalil, et al. *Clin Pharmacokinet* 2019;**58**:235–262
3. Gilead Sciences, Inc. Product Information: tenofovir disoproxil fumarate (VIREAD) tablets.
4. Hirt D, et al., *Clin Pharmacol Ther* 2009; **85**: 182–9.
5. De Sousa Mendes, et al., *Br J Clin Pharmacol* 2016;**81**(4):646–57.

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P02 ALLOPURINOL COUNTERACTS INADEQUATE MERCAPTOPYRINE 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/8x10⁸ 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/8x10⁸ 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 morbidity-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