available, together responsible for 36 area under the concentration-time curves (AUCs) and trough concentrations. First, hematocrit-corrected concentrations were derived using a formula describing the relationship between whole blood concentrations, hematocrit, and plasma concentrations. Subsequently, target exposure was evaluated using the converted plasma target concentrations. Ultimately, differences in interpretation of target exposure were identified and evaluated.

**Results** In total, 92% of our patients had a lower hematocrit (median 0.29) than the reference value of adult renal transplant patients. A different evaluation of target exposure for either trough level, AUC or both, was defined in 42% of our patients, when applying hematocrit corrected concentrations.

**Conclusion** A critical role for hematocrit in therapeutic drug monitoring of tacrolimus in pediatric kidney transplant patients is suggested in this study. Therefore, we believe that hematocrit correction could be a step towards improvement of tacrolimus dose individualization.

**Disclosure(s)** All authors declare that they have no conflict of interest.

This work was recently accepted for publication in Pediatric Nephrology. We are aware of the statement in the guideline about previously published work, however as we believe that this work suits the aim and topics of the congress very well, we chose to submit this work and will of course leave the final decision to you.

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**P89**

**EMICIZUMAB DEVELOPMENT IN PAEDIATRIC PATIENTS WITH CONGENITAL HEMOPHILIA A AND INHIBITORS AGAINST FACTOR VIII**

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**Background** Emicizumab, a bispecific monoclonal antibody, bridges activated factor (F) IX (FIXa) and FX, restoring missing FVIII function in patients with hemophilia A (PwHA). It has been recently approved for routine prophylaxis of bleeding episodes in PwHA with FVIII inhibitors in all age groups. We herein describe the paediatric development of emicizumab with a focus on dose selection, study design and extrapolation of efficacy.

**Methods** The dosing regimen for the HAVEN 1 study (adolescents/adults) was selected based on the exposure-response (annualized bleeding rate [ABR]) relationship derived from a phase I/II study in adolescent/adult PwHA. Pharmacokinetic (PK) simulations, with or without maturation of clearance (CL MAT), were performed to guide selection of the dosing regimen for the HAVEN 2 study (paediatrics) aiming to achieve the same target exposure as in HAVEN 1. HAVEN 2 employed a flexible design with possibility for individual- and population-level dose up-titration. Additional PK modeling and simulations together with exposure-response analyses were used to support full extrapolation of efficacy in any age category where no data was available.

**Results** 1.5 mg/kg/week in HAVEN 1 provided mean trough concentrations of ~50 μg/mL and was associated with a 87% reduction in ABR. Doses of ≥1.5 (with CL MAT) and ≥2.25 mg/kg/week (without CL MAT) were predicted to achieve this target exposure in children. HAVEN 2 began by investigating the same dose as HAVEN 1. Similar trough concentrations of ~50 μg/mL were achieved in children and were associated with low ABR. No patients < 1 year were enrolled in HAVEN 2. PK simulations and pharmacological rationale suggested that a different dose for these patients was not warranted.

**Conclusions** Efficacy of emicizumab in adolescents/adults was demonstrated in HAVEN 1, partially extrapolated to HAVEN 2 participants 1–11 year of age, and fully extrapolated in patients < 1 year.

**Disclosure(s)** Authors are Roche/Genentech employees

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**P90**

**NEUROPSYCHIATRIC DISORDER AND MONTELUKAST: A CASE REPORT AND VIGIBASE® ANALYSIS**

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**Learning objective** Recognize neuropsychiatric symptoms as possible adverse drug reactions (ADR) associated with the leukotriene receptor antagonist Montelukast in children

**Clinical Case** An 11-year-old boy suffering from asthma presented to his pediatrician with an acute onset of nervousness, restlessness and irritability. The teacher noticed a decline in school performance with a reduced attention span. The patient had been treated with Salbutamol (Ventolin®) and Salmeterol/Fluticasone (Sereide®) for the last few years. A treatment with Montelukast chewable tablets was started four months ago. The ADR was reported to the Regional Pharmacovigilance Centre (RPVC) Bern. The termination of the therapy with Montelukast lead to an amelioration of the symptoms. According to the WHO-UMC Causality Categories, the causality of Montelukast and the described symptoms was classified as ‘probable’. The causality of the comedication was considered ‘unlikely’ as it had been used for several years without complications. After work-up at the RPVC, the case was reported anonymously to the National Pharmacovigilance Center of the Swiss Agency for Therapeutic Products Swissmedic.

**Discussion** Montelukast is a cysteinyl-leukotriene type 1-receptor antagonist used in the treatment of bronchial asthma in adults and children. Psychiatric disorders such as agitation, psychomotor hyperactivity (including irritability and restlessness), disorders of attention and memory impairment (and others) are listed as known ADRs of Montelukast. The WHO pharmacovigilance database VigiBase® lists a total of 20897 ADR reports for Montelukast, of which 4705 (22.5%) refer to nervous system disorders and 6828 (32.7%) to psychiatric disorders. Within the group of nervous system disorders 256 (5.4%) reports of psychomotor hyperactivity, 232 (4.9%) reports of disturbance in attention and 91 (1.9%) reports of memory impairment were recorded. The most common symptoms in the group of psychiatric disorders are depression (1311, 19.2%) and aggressive behavior (1175, 17.2%). If psychiatric ADRs occur, the risks and benefits of Montelukast should be reassessed.
Introduction ACE inhibitors (ACEi) have a prominent place in the treatment of heart failure in children. However, there is a significant interpatient variability in efficacy and safety in those children that is not completely understood. Metabolomics provides an interesting innovative approach to better understand underlying mechanisms for variation in disease and response to therapy. With this review, we aim to provide an overview of metabolomics in the field of heart failure therapy with or without ACEi in both adults and children and try to identify gaps in this field.

Methods The PubMed database was systematically searched using several search strategies. Articles were labelled as relevant when they included information on either metabolomics of adult patients with heart failure and/or ACEi-therapy or in children. This yielded 42 relevant articles.

Results 24 articles were found describing metabolomics in adults with heart failure, either with or without ACEi-therapy. In addition, several metabolites were identified in adults correlating with either ACEi-efficacy or safety. No metabolomics articles were found in children with heart failure or in children on ACEi-therapy. Several papers (18) were found on metabolomics in children for other diseases and/or treatments.

Conclusion Metabolomics in adult heart failure patients has helped to unravel part of observed disease and therapy variability, and appears helpful in identifying patients at risk for therapy failure as well as detecting novel targets for heart failure therapy. In children, a significant information gap exists. This provides exciting opportunities for personalized treatment of heart failure.

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