P116 | SEROPREVALENCE OF PRE-EXISTING NABS AGAINST AAV1, 2, 5, 6 AND 8 IN SOUTH AFRICAN HEMOPHILIA B PATIENT POPULATION

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Introduction: Extensive surveys on the prevalence of anti-AAV antibodies in humans have been published indicating that prevalence varies dependent on serotype, and that a significant proportion of individuals develop humoral immunity against various AAV serotypes early in life, starting around 2 years of age. Furthermore, the prevalence of antibodies to different AAV serotypes has been reported to vary according to geographical location. We performed a neutralizing antibody seroprevalence study in South African hemophilia B patient population (n = 44) using a panel of AAV serotypes suitable for liver targeted therapy, to determine the AAV serotypes likely to be of greatest clinical applicability for the South African hemophilia B population.

Methods: Forty-four hemophilia B patient serum samples were obtained from Hemophilia Comprehensive Care Center in Johannesburg (South Africa). All the patient serum samples were analyzed for the presence of NABs against AAV serotypes 1, 2, 5, 6 and 8 with the use of highly sensitive luciferase-based bioassays.

Results: The highest prevalence of NABs was found to be against the AAV2 serotype, 95% (n = 42/44) followed by the AAV6 serotype, 82% (n = 36/44), and the AAV1 serotype 77% (n = 34/44). The prevalence of NABs against AAV5 and AAV8 was lower with 66% (n = 29/44) for AAV5 and 64% (n = 28/44) for AAV8. Serum samples positive for anti-AAV2 NABs had a high occurrence of titers above 1030 (39%) in comparison to anti-AAV1 NABs (21%), anti-AAV5 NABs (5%) or anti-AAV8 NABs (7%).The occurrence of samples with low titers (ranging from titer of 8 to titer of 50) was the highest for anti-AAV8 NABs (32%) and for anti-AAV5 NABs (27%), followed by anti-AAV2 (18%) and anti-AAV1 (6%)

Discussion/Conclusion: Currently, an anti-AAV NABs titer of 5 is used as an exclusion criteria in most of the systemic AAV-based gene therapies. When applying the cut-off of 5, 23% of the analyzed patients could be treated with AAV1, 5% with AAV2, 34% with AAV5, 18% with AAV6 and 36% with AAV8-based therapeutics. However, we have previously reported that AAV5-neutralizing antibodies do not impair the efficacy of in vivo transduction of AAV5-based vector up to a measured titer of 340 in humans and 1030 in non-human primates. Therefore, applying the cut-off of 340 or 1030, either 84% or 95% of the South African Hemophilia B patients could benefit from treatment with AAV5-based gene therapy

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P117 | PK-GUIDED SWITCH BETWEEN STANDARD HALF-LIFE AND EXTENDED HALF-LIFE FACTOR VIII PRODUCTS

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Introduction: Extended half-life (EHL) factor VIII (FVIII) requires improvements in half-life ($t_{1/2}$) & area under the curve (AUC) of 1.3 & 1.25 times compared to standard half-life (SHL) products. The aim of this study is compare pharmacokinetics (PK) after the switch from SHL to EHL in patients with hemophilia A (HA).

Methods: Multicenter comparative, cross-sectional, prospective study analyzing PK differences after switch from SHL to EHL (efmoroctocog alfa [rFVIII-Fc] & rurioctocog alfa pegol [PEG-rFVIII]). WAPPS-Hemo® was used to analyze PK parameters with 2-3 samples: $t_{1/2}$; AUC, peak level (PL); trough level at 24, 48 & 72 hours (TL24, TL48, TL72); & time to reach FVIII levels of 1, 2, 5% (T1%, T2%, T5%). Ratio of $t_{1/2}$ & AUC, the number of weekly doses & the dose/kg/week before & after the switch were compared. Wilcoxon & Kruskal-Wallis tests (SPSS®) were used to compare the PK parameters.

Results: Eighty-three patients from 8 Spanish hospitals were analyzed (62 rFVIII-Fc; 21 PEG-rFVIII), 79 had severe HA & 4 moderate HA. Median age was 30 years (range = 3-64) & no differences in weight were observed between both periods.

Dose/kg/week & weekly infusion frequency were reduced after the switch to EHL, & significant improvements were observed in all PK parameters after the change from SHL to EHL (Table 1). The median ratios of $t_{1/2}$ & AUC were 1.3 (IQR:1.2-1.6) and 1.6 (IQR:1.3-2.2) in the entire cohort. In patients with ≥12 years ratios of $t_{1/2}$ & AUC were 1.4 (IQR:1.3-1.6) & 1.7 (IQR:1.3-2.3), and in the cohort of 16 patients <12 years treated with rFVIII-Fc were 1.3 (IQR:0.9-1.5) and 1.4 (IQR:1.1-2.1).

After the switch to EHL, median weekly dose frequency (30%, IQR:0-33.3%) & dose/kg/week (16.9%, IQR:8.7-32.8%) were reduced. In a small subset of 15 younger patients the dose/kg/week was increased a median of 28.6% (IQR:11.7-40-7%). No differences

were observed in any of the PK parameters & median ratios of $t_{1/2}$ & AUC in patients aged ≥12 years treated with rFVIII-Fc vs. PEG-rFVIII (46 rFVIII-Fc; 21 PEG-rFVIII).

Discussion/Conclusion: EHL FVIII have shown significant PK improvements in clinical real practice, allowing to reduce weekly infusion number & dose/kg/week. Outside the clinical trial setting, we have observed an increase in $t_{1/2}$ & AUC ratios accordingly to EHL definition. Comparisons regarding clinical outcomes (bleeding rate after switch) will be performed after a follow-up of 1 year with EHL for the full cohort.

Disclosure of Interest:

None declared. :

P118 | CIRCUMCISION OPERATION WITHOUT USING BY-PASSING AGENTS IN PATIENT WITH HIGH RESPONDER INHIBITOR WHILE HE WAS IN WEEKLY EMICIZUMAB PROPHYLAXIS

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Introduction: Circumcision in the most frequent surgical procedure for hemophiliac patients in Muslim and Jewish societies. Social integrance of hemophilia patient is very important approach that we help these patients to be circumcised in safety conditions even having a bleeding disorder. We use "Izmir protocol" for circumcision for more than 20 years. Fibrin Glue is main stone and two days of factor substitution are used in hospitalization after general anesthesia. However inhibitor positivity is contradictory for Izmir protocol due to inefficacy risk with by-passing agents. We generally postpone the operation and waiting after eradication of inhibitor with ITI program.

Methods: However for this present case, we planned the elective operation while he was using weekly emicizumab prophylaxis for 2.5 years in the extension program for HAVEN-2. We prefer to use orally tranexamic acid for 7 days and Fibrin Glue application during operation as well. Recombinant FVIIa (NovoSeven) application was preserved for potential post-op bleedings. aPCC was not already selected according to clinical trial protocol.

Results: Twelve year old boy and severe hemophilia-A (FVIII < 1%) and HR inhibitors (12 BU/mL) for last 6 years. Using general anesthesia, circumcision operation was completed without bleeding only using perioperative Fibrin Glue (Beriplast, Behring) application. Tranexamic acid also completed for 7 days perorally. Any by-pass agents were used before, during or after the operation.

Discussion/Conclusion: This case report is very important that for hoping other Turkish patients with inhibitor who were waiting many years for circumcision operation. Ministry of Health was recently approved and in a cup of months reimbursement will be initiated for inhibitor patients. Interestingly circumcision operation for inhibitor patients is evaluated as major operation more than minor procedure. Emicizumab showed its well known efficacy during and after operation. And any safety problems were observed.

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P119 | CLINICAL MANAGEMENT OF WOMEN WITH BLEEDING DISORDERS: RESULTS OF A SURVEY AMONG EUROPEAN HEMOPHILIA TREATMENT CENTERS

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Introduction: Issues faced by women with inherited bleeding disorders (WBD) were emphasized in a recent European Hemophilia Consortium (EHC) patient survey. The EAHAD WBD Working Group aims to gather knowledge and define research priorities on diagnosis and management of WBD.

Methods: From 9 May-3 July'19 an electronic survey on the multidisciplinary management of heavy menstrual bleeding (HMB) and pregnancy was sent to 136 certified European hemophilia treatment centers (HTCs), including open questions to identify clinical knowledge gaps and research priorities. Differences in proportions were tested with Chi2.

Results: 59 HTCs from 12 Western (WE) and 13 Central/Eastern European (CEE) countries completed the survey.

A joint clinic where female patients can consult with a hematologist, obstetrician and gynecologist, nurse, psychologist/social worker, etc. during one visit exists in 24 HTCs (42%). Reported barriers to organize a joint clinic are most often institutional (n = 20), followed by physician imposed barriers (such as lack of interest or knowhow, n = 14) and financial barriers (n = 10). None of the respondents identified lack of interest among patients as a barrier. Most centers without a joint clinic do have a named obstetrician (81%) and/or gynecologist (75%) available for collaboration.

Overall 18/54 (33%) European HTCs do not offer pre-implantation genetic diagnosis. Third trimester amniocentesis to guide obstetric