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SIMTI Società Italiana di Medicina Trasfusionale e Immunoematologia

AICE Associazione Italiana dei Centri Emofilia

HDTM Hrvatsko Društvo za Transfuzijsku Medicinu

SETS Sociedad Española de Transfusión Sanguínea y Terapia Celular

SISET Società Italiana per lo Studio dell'Emostasi e della Trombosi

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ABSTRACT BOOK

XVII Convegno Triennale sui Problemi Clinici e Sociali dell'Emofilia e delle Malattie Emorragiche Congenite

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Edizioni SIMTI

Blood Transfusion - Bimestrale spedizione in abbonamento postale 70% - Poste Italiane SpA LO/MI

2.08 - PHARMACOKINETICS

ABS37 - Genotype and PK Hemophilia B International Study (GePKHIS) - A progress Report

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Background. Acquired and congenital components of the ample inter-patient variabilily in factor IX (FIX) pharmacokinetic (PK) parameters have been poorly defined. The main study hypothesis is that *F9* mutations could influence PK parameters through the endogenous biosynthesis of mutated FIX variants.

Methods. Hemophilia B (HB) patients enrolled in the AICE centers were characterized in relation to recombaint (r)FIX (Nonacog Alpha) PK analysis and *F9* mutations. Patients' *F9* mutations were recombinantly expressed, and secreted rFIX variants investigated for FIX:Ag and FIX:C levels.

Results. We have expressed 18 different *F9* mutations detected in patients, and in addition 15 rationally designed and topologically equivalent *F9* mutations. Mutations, and the associated FIX antigen expression values, have been grouped in relation to their type. Among missense mutations, special attention was paid to those affecting the FIX activation sites (R191 and R226), and the effects on FIX secretion and activity of natural and artificial substitutions in these sites were compared in relation to PK parameters in patients affected by mutations at the 191 and 226 sites.

Conclusions. We have explored the hypothesis that mutations in the FIX activation sites could be related to better PK parameters with SHL rFIX. The preliminary data obtained support the GePKHIS main aim, to provide evidence for the influence of specific *F9* mutations on PK of rFIX infused to treat HB patients, exerted by the residual amounts and quality of the mutated endogenous FIX.

ABS38 - The asialoglycoprotein receptor ASGR2 5' UTR polymorphisms influence several parameters of full-length FVIII concentrate pharmacokinetics

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Background. The asialoglycoprotein receptor (ASGPR) binds with high affinity the factor VIII (FVIII) B domain, particularly through its N-linked oligosaccharide structures. Evidences in mouse models support a role for this receptor in the VWF and FVIII clearance. The human oligomeric receptor is composed of major (ASGPR1) and minor (ASGPR2) subunits. Alternative splicing of the *ASGR2* mRNA originates multiple RNA transcripts, potentially encoding transmembrane and soluble isoforms and differing among individuals.

We investigated the relation between the potentially regulatory *ASGR2* 5' UTR polymorphisms and patient variability in FVIII pharmacokinetic (PK) outcomes.

Methods. Twenty-eight hemophilia A (HA) patients with FVIII:C ≤ 2 IU/dL underwent 55 FVIII single dose (22.7-51.8 IU/Kg) PKs using pd-FVIII and/or FL r-FVIII concentrates. FVIII:C was measured up to 72 hours and analyzed by two-compartment PK model. PK parameters

were evaluated in relation to *F8* mutations, *ABO* blood-group and eight polymorphisms in the *ASGR2* 5' UTR, investigated by sequencing.

Results. Patients grouping by the *ASGR2* g.5173T/C (c.-95T/C) and *ABO* genotypes displayed several significant differences in PK parameters. The c.-95 TT homozygotes (n=9) differed from homozygotes and carriers of the C allele (n=19) for the K 1-2 (P=0.048), K 2-1 (P=0.021), Alpha (P=0.022), Alpha HL (P=0.01) and CLD2 (P=0.046) parameters. Homozygotes (n=5) for the common TT haplotype (H1), including the most frequent 5' UTR alleles conserved in primates, showed significantly lower K 1-2, Alpha and CLD2 values, and higher Alpha HL values than the CC homozygous genotypes.

In linear regression models including the *ASGR2* c.-95T/C and *ABO* genotypes, with PK parameters as dependent variables, the K 2-1, Alpha and Alpha HL parameters were significantly predicted by the *ASGR2* c.-95T/C (P=0.032, β coefficient 0.373; P=0.033, β coefficient 0.401 and P=0.016, β coefficient -0.426, respectively). In the non-O patients (n=19) the *ASGR2* c.-95T/C genotypes were associated with a significant gradient of K 1-2 (P=0.032), K 2-1 (P=0.042), Alpha (P=0.020), Alpha HL (P=0.011) and Clearance (P=0.045) values.

Conclusions. Several parameters of full-length FVIII PK in HA patients were significantly associated with frequent *ASGR2* c.-95T/C genotypes also after correction for *ABO* genotypes. The homozygous *ASGR2* c.-95TT genotype noticeably improved PK parameters in non-O blood group patients. The relation between the *ASGR2* H1 haplotype and specific RNA transcripts with FVIII PK parameters remains to be established.

2.09 - PROPHYLAXIS

ABS39 - The evolving treatment of haemophilia B: real-life experience with rIX-FP

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Background. Extended half-life (EHL) recombinant Factor IX (rFIX) products enabled prophylaxis in haemophilia B (HB) patients with infusions every 7-14 days, reducing treatment burden and concentrate consumption compared to standard half-life (SHL) FIX. Few studies currently document the real-life adoption and efficacy of EHL rFIX prophylactic regimens. We here report data from patients switched to albutrepenonacog alfa, a EHL rFIX-albumin fusion protein (rIX-FP).

Methods. Data collection included pharmacokinetic (PK) studies (50 IU/Kg rFIX-FP, ≥96 h wash-out, FIX:C at baseline up to 240h after infusion) and clinical and laboratory assessments in patients switching to rIX-FP (bleeding and infusion report, FIX:C through and inhibitor; monthly for 3 mo, every 3 mo for further 9 mo, then every 6 mo) from market availability to Feb 2020. For patients previously on SHL-FIX prophylaxis, rIX-FP data were compared with those from 2 yrs before switch.

Results. Twelve patients (10 severe, 2 moderate; age, mean±1SD, 36±15 yrs) switched to rIX-FP, i.e. all HB patients previously on prophylaxis and 92% of those with indication to prophylaxis (67% on SHL rFIX). Indeed, 3 patients (2 severe) started prophylaxis with rIX-FP, previously unfeasible due to venous access or home treatment problems. At PK analysis (n=10), mean half-life was 85.5±8.3 h. Mean prophylactic dose was 46±7 IU/Kg, every 7 (n=5), 10 (n=6) or 14 d (n=1). All patients but one remained on rIX-FP, for mean 22±11 mo. Over follow-up, 7 patients prolonged infusion intervals and all but one (a 12-yr boy) achieved every ≥10 d-dosing regimens, being mean trough FIX:C 8.5±1.7%. Annualized bleeding rates (ABR) was 0.9±1.1, higher than on SHL FIX (0.3±0.4, p=0.02), but unchanged for joint and spontaneous