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BLOOD TRANSFUSION

OFFICIAL JOURNAL OF

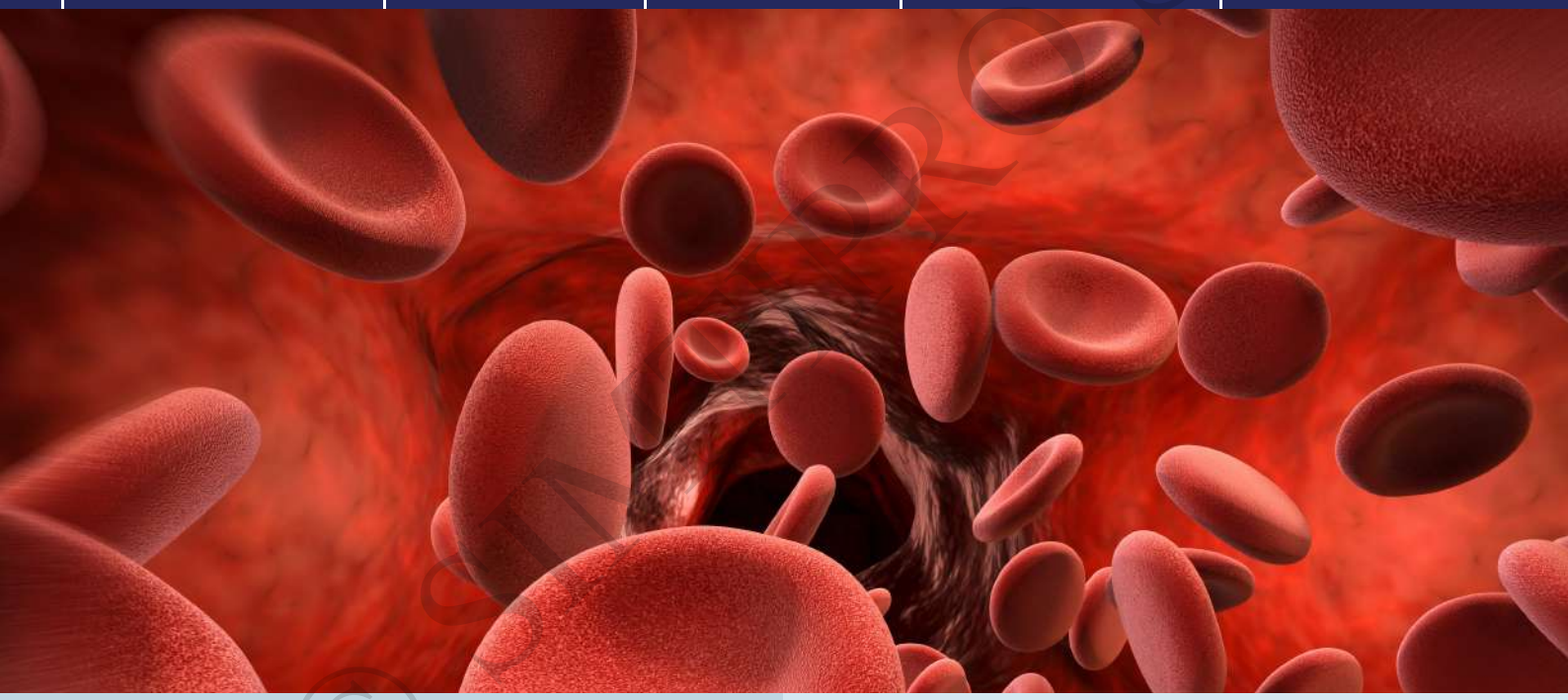
SIMTI Società Italiana di Medicina Trasfusionale e Immunoematologia

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



Blood Transfus 18, Supplement no. 3, October 2020

-ISSN 1723-2007-

ABSTRACT BOOK

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

Milano, 8 - 11 ottobre 2020

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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