Pharmacokinetics of Factor VIII in Patients with Hemophilia A in Relation to Clinical and Radiological Outcomes

Thesis

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List of Abbreviations

Abb.	Full term
ADH	Antidiuretic hormone
APC	Active protein C
APTT	Activated partial thromboplastin time
ASA	Acetylsalicylic acid
AUC	Area under curve
BDD FVIII	B-domain-deleted FVIII
BDD	B-domain-deleted
BSA	Bovine serum albumin
BU	Bethesda units
CFC	Coagulation factor concentrates
CL	Clearance
CSAs	Chromogenic substrate assays
CT	Computed tomography
DDAVP	Desmopressin (1-deamino-8-D-arginine vasopressin)
EACA	Epsilon aminocaproic acid
ECAT	External quality Control of diagnostic Assays and Tests
EHL	Extended half-life
FDA	Food and Drug Administration
FFP	Fresh frozen plasma
FISH	Functional Independence Score for Hemophilia
FIX	Factor IX
FVIII	Factor VIII
FVIIIa	Activated FVIII
FX	Factor X
FXa	Activated FX
FXIa	Activated FXI

List of Abbreviations Cont...

Abb.	Full term
HEK	Human embryonic kidney
Ig	Immunoglobulin
IU	International units
IVR	In-vivo recovery
MR	Magnetic resonance
MRT	Mean residence time
NONMEM	Nonlinear mixed effects modeling
NSAIDs	Non-steroidal anti-inflammatory drugs
OSAs	One stage Assays
PD	Pharmacodynamics
PEG	Polyethylene glycol
PK	Pharmacokinetics
PT	Prothrombin time
PTT	Partial thromboplastin time
rFVIII	Recombinant factor VIII
r-FVIII	Recombinant FVIII
rFVIII-Fc	Antihemophilic factor (recombinant), Fc fusion protein
rFVIII-FS	Recombinant FVIII formulated with sucrose
rFVIII-SC	Antihemophilic factor (recombinant), single chain
SC	Single chain
US FDA	US Food and Drug Administration
VD	Volume of distribution
VWF	Von Willebrand factor
Vss	Volume of distribution at Steady State

INTRODUCTION

Hemophilia is an X-linked congenital bleeding disorder caused by a deficiency of coagulation factor VIII (FVIII) (in hemophilia A) or factor IX (FIX) (in hemophilia B) **(White et al., 2001).** Estimations based on the WFH's annual global surveys indicate that the number of people with hemophilia in the world is approximately 400,000 **(Stonebraker et al., 2010).**

Prophylaxis is the treatment by intravenous injection of factor concentrate in order to prevent anticipated bleeding. Prophylaxis was conceived from the observation that moderate hemophilia patients with clotting factor level >1 IU/dl seldom experience spontaneous bleeding and have much better preservation of joints function. According to a review of 6 randomized controlled trials, preventive therapy started early in childhood, as compared with on-demand treatment, can reduce total bleeds and bleeding into joints, resulting in decreased overall joint deterioration and improved quality of life **(Feldman et al., 2006; Gringeri et al., 2011).**

However, the optimal dosing and infusion frequency to reduce bleed risk and enable participation in routine daily and physical activities is debated. **(Fischer et al., 2013)**

The benefit of pharmacokinetics (PK) -guided dosing is that both prophylactic and “on demand” dosing will be based on actual FVIII trough and peak levels instead of current FVIII estimates based on body weight and in-vivo recovery (IVR)

based dosing. Moreover, PK-guidance will optimize dosing as knowledge will increase with regard to the relationship between FVIII level and bleeding in individual patients. In addition, an increase in dosing will not only depends on actual bleeding and a reduction of dosing can be considered by the treating professional in consultation with patients and parents. However, the dose and frequency of factor VIII for patients on prophylaxis should only be reduced if clinically justified and impact should be monitored with regard to bleeding events, bleeding pattern and joint status **(Berntorp et al., 2017).**

We believe that PK-guided dosing as the alternative to body weight and IVR-based dosing will play an important role in further individualization of therapy.

Aim of the Work

To assess the trough and peak level of factor VIII in patients with hemophilia A on low dose prophylaxis and to study its impact on the clinical and radiological joint status.