Extended Half-Life (EHL) proteins and Pharmacokinetics Working Group

Subcommittee: FVIII/FIX/RBD SSC: EHL & PK Working Group

Date: April 28, 2017

- Person responsible (Chair / Principal Investigator): Margaret Ragni, MD, MPH
- Design: Survey, Literature Review, Evolving Clinical Experience, PK Model Data, Expert Opinion
- Aim/Objective/Rationale (Needs assessment / Reason):
  **AIM:**
  To focus on and define the use of pharmacokinetics in patients treated with extended half-life (EHL) proteins

  **OBJECTIVES:**
  1) To define in whom, when, and under what circumstances, should PK be done.
  2) To determine the PK parameters that should be obtained, including minimum and optimal information to inform EHL use.
  3) To review, describe PK models are available (e.g. OPTI-CLOT, WAPPS, myPKfit / SHIRE)
  4) To discuss and define how PK should be interpreted.
  5) To determine how PK results should be implemented into treatment.
  6) To assess patients’ compliance to home PK.

  **RATIONALE:**
  Accumulating clinical experience and data with EHL indicate there is no standard approach to sampling, implementation, and interpretation of PK data to manage patients using EHL proteins. The charge to this WG Is to define an approach to the use of PK parameters, sampling frequency, and PK models that will maximize efficiency in the clinic and provide optimal patient outcomes with the use of EHL proteins.

  Note: this group is aware of the ongoing work of the PK and PopPK subgroup of the ISTH SSC on FVIII/FIX/RBD and of the potential overlap on objectives 1, 2, and 4. We will harmonize the output of our group with other groups, discuss and discrepancies to help the reader understand the reasons for any differences which may exist.

- Methodology (Data expected to collect, sample size and statistical analysis):
  1) Develop and distribute a survey of hemophilia centers regarding current use of PK to manage patients initiating EHL, which PK parameters are used, when, and how used.
  2) Perform literature review of EHL and PK studies.
3) Obtain PK data from PK models published in manuscripts, or if not previously available, from pharmaceutical trials.
4) Grade the evidence by level, grade.
5) Review, summarize, and analyze data, by descriptive statistics, chi-square, t test, meta-analysis, regression analysis, as appropriate.
6) Determine recommendations based on data, analysis, expert opinion.
7) Write manuscript, circulate for review by group, submit to JTH as SSC report.

- **Study population** (Inclusion, exclusion, eligibility) (patient population; recruitment of participating institutions/physicians and subjects; minimum number needed; expected number):
  1) Inclusion: Hemophilia A, B patients initiating EHL, including patients with past inhibitors who have cleared them by ITI or spontaneously. FVIII.
  2) Exclusion: Inhibitor patients with active inhibitors, considered for ITI, or treated only with bypassing agents.
  4) Sample will be based on available data from literature, pharma, survey.
  5) Additional data from PK models, where possible.
  6) The relationship between PK and FVIII/IX or other gene polymorphisms

- **Expected timeline:**
  o Project stage/set up: Literature selected, writing assignments made ~ May 2017
  o Launch: May 2017
  o Duration: 6 months ~ October 2017
  o Finalization/analysis: 6 months ~ January 2018
  o Reporting: May 1 2018

- **Expected outcomes** (i.e. publications):
  o Publication type: SSC Guidance document of the EHL&PK WG

- **Description of project set/up and management, needed infrastructure and resources.**
  The purpose of this project is to develop guidance on the implementation of PK to optimize use of EHL in individuals with hemophilia, including patients with past inhibitors who have cleared them by ITI or spontaneously. This WG will gather data by survey center PK practice, literature review, PK models (OPTI-CLOT, WAPPS, myPKfit), pharmaceutical data (if not previously available), and expert opinion. The goal will be to provide high level evidence to inform the optimal approach and implementation of PK for EHL use in clinical practice.

Within OPTI-CLOT, we are preparing a practical advice schema for the Dutch hemophilia treaters, including how to do a PK profile at the introduction/switch to new EHL product. If the OPTI-CLOT group agrees, this plan will be shared with the EHL&PK group. We could perfect the schema by incorporating the WAPPS EHL data, as it becomes available.

- **Possible references:**


12. Other: tentative
   c. Iorio A, WAPPS data (in preparation).