Choosing factor VIII source when starting treatment in a patient with hemophilia A

This document aims to prepare the clinician to discuss scientific evidence with the patient (or care takers) so they can make an informed decision together.

What is factor VIII concentrate and how is it used to treat hemophilia?

Hemophilia A patients need to receive intravenous factor VIII concentrate (FVIII) to restore normal coagulation and thus stop or prevent bleeding. FVIII may be prepared from **plasma** (pdFVIII, as a by-product of a blood donation) or produced in molecular biology laboratories from **recombinant** DNA technology (rFVIII). As for any other medication, the specific FVIII concentrate used by a patient can be changed with time if needed or wished, but the choice for the molecule to be used as initial treatment is an important one. This document will help discuss the choice between the two broad categories of pdFVIII and rFVIII. Long acting factor concentrates will be added, when available.

Why do patient/parent preferences matter when making this decision?

While both treatments have a similarly high efficacy in controlling and preventing bleeding, the choice should take into account the patients/parents' **values and preferences** regarding:

- Pathogen safety, i.e. regarding risk of blood borne infection
- Immunogenicity, i.e. risk of developing neutralizing inhibitors
- Availability and cost-related issues.

Selection of the best available studies (January 2013)

Option	Benefits	Risks
Plasma-derived (pdFVIII)	**Inhibitor development** Some studies suggest a lower risk of inhibitors in pdFVII as compared to rFVII (see table on reverse).	**Blood borne infections** Major procedural advancements have resulted in **no** documented blood-borne transmission of HIV since 1987[3] or hepatitis viruses since 1991[4], however there are still *potential* risks of becoming infected with: • Yet-unknown and emerging pathogens[5], for example, non pathogenic viruses like human parovirus (PARV4, detected in 9% of pdFVIII products[6]) and transfusion transmitted virus (TTV, isolated from some batches of pdFVIII products[7]) survive current inactivation processes. • Variant Creutzfeldt-Jacob disease: a single case among hemophiliacs reported in the United Kingdom (UK).[8] **Availability** Safety procedures related to blood donor surveillance may lead to delay in releasing batches of pdFVIII with temporary shortage of products.[3]
Recombinant (rFVIII)	**Risk of blood borne infections** Since rFVIII are produced without using human products, the risk of transmitting infections is virtually zero,[1,2] as confirmed by 20 years of observation.[3] **Availability** There is no theoretical reason to expect a shortage of rFVIII as a class; and most molecules are produced at higher volume than requested on the market.	**Zoonotic Infections** Animal cells used to produce rFVIII might be infected by animal viruses, with theoretical risk of transmission to receipients.[9] Such an event has never been reported. **Risk of inhibitor development** Some studies suggest a higher risk of inhibitors in rFVIII as compared to pdFVIII (see table on reverse).

Risk of inhibitor development: selected studies

Study	Design	rVIII	pdVIII	Notes
Wight 2003[10]	Systematic review	Range: 36 - 39%	Range: 0 - 12%	13 uncontrolled case series; no direct comparisons
Calvez 2007[11]	Systematic review	Range: 27 - 36%	Range: 11 - 21%	4 retrospective uncontrolled case series - 1 retrospective cohort (29 vs 21)
Iorio 2010[12]	Systematic review	Range: 3 - 36%	Range: 3 - 50%	24 uncontrolled case series; most of the variability explained by confounders at multivariable analysis
EUHASS 2012[13]	Prospective observation PUP*=209 PTP*=>4000	Mean (95% CI) PUPs: 26% (21 - 32) PTPs: 19% (11 - 31)	Mean (95% CI) PUPs: 15% (6 - 30) PTPs: 22%% (10 - 44)	Prospective parallel observation
RODIN 2013	Prospective/ retrospective cohort	145/476 (31%) Note: second generation full-length products might have 60% higher risk than third-generation products	29/88 (33%)	Retrospective/ prospective

*PUP=previously untreated patient; PTP=previously treated patient

How much confidence can we have in the evidence for this decision?

Blood borne infections. After the dramatic epidemics of blood borne HIV and hepatitis C virus (HCV) infections in the 1970s and 1980s, there has been no further case of infection reported. Notwithstanding the theoretical low quality evidence originating from (absence of) spontaneous reports, in the specific case of hemophilia, and in view of the high level of attention devoted to surveillance and the almost ubiquitous common practice of recurrent testing for infections, we are very certain that infection cases have not been passed unobserved and have not happened at all.

Inhibitors. There is low quality evidence regarding the risk estimates of **inhibitor development** because the results are based on observational uncontrolled case series. Iorio and colleagues[12] showed how much the difference in study designs can account for the observed differences in inhibitor rate in different studies. Looking at the more convincing studies, the difference in inhibitor rates seems to be minimal if any, and mostly due to transient (self-resolving) inhibitors (Iorio[12], EUHASS[13], CANAL[14],RODIN[15]). Ongoing studies like the Survey of Inhibitors in Plasma-Product Exposed Toddlers (SIPPET)[16] will provide a definitive answer to this question.

Body of available evidence. While pdFVIII and rFVIII have been shown on clinical ground a similar efficacy (Blanchette 2008),[17] most rVIII concentrates have been undergoing a more controlled development and approval process, and are consequently supported by better quality evidence, with more patients followed up in a formal way in registration and post-marketing studies.[3] In particular, pediatric data are more abundant for rFVIII which has been used extensively as drug of first choice in several locations, as recommended by major guidelines (UK, Italy, Sweden, Canada, Netherlands, Australia, MASAC).[3] It has to be acknowledged that the recently updated World Federation of Haemophilia (WFH) guidelines do not express a preference for source of concentrate.[18]

References: [1]Fricke W *Transfusion* 1992; [2]Lusher JM *NEJM* 1993; [3]Hermans C *Crit Rev Oncol Hemotol* 2012; [4]Soucie JM *Transfusion* 2001; [5]Luban NLC *Semin Hematol* 2003; [6]Schneider B *Haemophilia* 2008; [7]Azzi A *Blood* 2001; [8]Peden A *Haemophilia* 2010; [9]Manucci PM *Blood* 2012; [10]Wight J *Haemophilia* 2003; [11]Calvez T *J Thromb Hemost* 2008; [12]Iorio A *J Thromb Hemost* 2010; [13]Makris M *EUHASS* 2012; [14]Gouw SC *Blood* 2007; [15]Gouw SC *NEJM* 2013; [16]Manucci PM *Haemophilia* 2007; [17]Blanchette VS *J Thromb Haemost* 2008; [18]Srivastava A *Haemophilia* 2013