Real-Life Pharmacokinetics of rFVIII-Fc and rFIX-Fc

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Extended half-life (EHL) products have made their way to clinical practice in the treatment of hemophilia A and B. Phase-3 studies indicated a significantly prolonged terminal half-life (T1/2) of rFVIII-Fc and rFIX-Fc versus standard rFVIII and rFIX: 19.0 versus 12.4 hours (1.5-fold) for FVIII and 82.1 versus 33.8 hours (2.4-fold) for FIX.1,2 In clinical practice and after switching to EHL are shown in -Table 1. T1/2 of rFVIII-Fc was extended 1.4-fold compared with rFVIII (p = 0.004). T1/2 of rFIX-Fc was extended 2.6-fold compared with rFIX (p = 0.005). A subgroup analysis showed shorter T1/2 for both rFVIII-Fc and rFIX-Fc in ex-inhibitor patients, with comparable half-life extension. Extension of T1/2 was age dependent: in children, T1/2 was extended 1.3-fold for rFVIII-Fc and 2.1-fold for rFIX-Fc versus 1.6- and 2.7-fold, respectively, in adults. The median time above 1% FVIII/IX activity after a prophylactic infusion was extended by 1.5 days for hemophilia A (p = 0.002) and by 10.2 days for hemophilia B (p = 0.005). After switching to EHL concentrates, the mean annual CFC dropped 10% in hemophilia A and 29% in hemophilia B patients, p = 0.04 (absolute numbers in -Table 1). A clinically relevant reduction of ≥10% was seen in 7 of 14 hemophilia A and in 7 of 13 hemophilia B patients (-Fig. 1). Children showed a more pronounced reduction in CFC than adults, especially children with hemophilia B. Prophylactic infusion frequency was reduced in a minority (4/15: 26.7%) of hemophilia A patients and in almost all (14/15, 93.3%) patients with hemophilia B, who were all able to infuse rFIX-Fc once weekly. ABR decreased in adults with hemophilia A only, from 4.0 to 2.1, (p = 0.05). For patients with hemophilia B, a trend toward ABR reduction was observed in children only, from 3.5 to 2.5, (p = 0.08).

This study demonstrates that the switch resulted in an extension of the terminal half-life of rFVIII-Fc (1.4-fold) and rFIX-Fc (2.6-fold) and a significant prolongation of the time to reach a trough level of 1% (1.5 days for hemophilia A and 10.2 days for hemophilia B) with a higher AUC. The infusion frequency of patients with hemophilia A remained stable. The resulting higher and more stable trough levels are expected to provide better protection against bleeds. The A-LONG phase-3 study in hemophilia A included 28 patients with hemophilia A >12 years who underwent PK assessments compared with 15 patients in our study (including 5 <12 years).1 The T1/2 increase...
of rFVIII-Fc in our real-life study (1.4-fold) was comparable with the phase-3 study (1.5-fold), as was the time to reach a trough level of 1% (4.2 vs. 4.9 days). For hemophilia B, the B-LONG phase-3 study included 22 patients aged >12 years who underwent PK assessments compared with 15 patients in our study (including 2 <12 years). The T1/2 increase of rFIX-Fc in our real life experience (2.6-fold) was similar to the phase-3 study (2.4-fold). Although the time to reach a trough level of 1% appeared longer in our study (17.4 vs. 11.2 days). This may be explained by differences in modeling and/or the shorter sampling time: 168 versus 240 hours in the phase 3-study. In patients <18 years, T1/2 observed (76.1 hours) was similar to the kids B-LONG study (68.6 hours).

Our switching protocol was prespecified and included standard testing, using prophylactic dosing to reflect the real-life experience and patient relevant outcomes. The present study had much longer follow-up than other real-life studies by Keepanasseril et al (6 months pre- and post-switch) and Wang and Young (1 year pre switch, 230 days postswitch) and reported both clinical and PK parameters.

### Table 1  Treatment characteristics and bleeding before and after switching to FVIII-Fc or FIX-Fc

|                      | Hemophilia A (n = 15) | Hemophilia B (n = 15) |
|----------------------|-----------------------|-----------------------|
| **Median (IQR)**     |                       |                       |
| **Age (y)**          | 29 (6–62)             | 39 (17–51)            |
| <18 years            | 40%                   | 33%                   |
| Blood group O        | 53%                   | 53%                   |
| **Duration of follow-up (mo)** | 24                  | 24                   |
| **Prophylactic dose/kg/infusion** | 16 (13–29)           | 16 (13–29)           |
| **Terminal half-life (h)** | 10.1 (8.8–12.9)      | 14.0 (11.5–18.3)     |
| **Estimated time to 1% (d)** | 2.7 (2.5–3.4)      | 4.2 (3.3–5.3)       |
| **AUC (IU*h/L)**     | 7,863 (6,589–10,678) | 13,629 (10,334–17,069) |
| **Clearance (mL/h/kg)** | 3.67 (2.73–4.25) | 2.14 (1.81–3.02) |
| **Cmax (IU/mL)**     | 0.77 (0.52–1.06)     | 0.75 (0.65–0.97)     |
| **Number of infusions per week** | 3.0 (3.0–3.5) | 3.0 (2.3–3.5) |
| **Annual bleeding rate** | 2.3 (0.9–7.5) | 1.9 (0.6–4.1) |
| **Mean (95% confidence interval)** |  |  |
| **Annual CFC (IU/kg/year)** | 3,578 (2,655–4,500) | 3,205 (2,414–3,996) |

Abbreviations: AUC, area under the curve; CFC, Clotting factor consumption; IQR, interquartile range.

*p < 0.05.

**Fig. 1** Change in clotting factor consumption.
In conclusion, this is the first real-life study reporting on both PK and clinical effects of rFVIII-Fc and rFIX-Fc. We observed significant half-life extension, similar to the phase-3 studies, together with a clear reduction in weekly infusion frequency in hemophilia B and lower annual CFC in both hemophilia A and B.

Note
The data was presented by a poster presentation at the ISTH Congress in Melbourne in July 2019.

Conflict of Interest
R.E.G.S. received an unrestricted grant from Sobi for this project.

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