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LETTER TO THE EDITOR

In response to WFH guidelines for the management of haemophilia, 3rd edition: Is there a difference between extended-half-life FVIII products or not?

Prophylaxis is now widely accepted as the standard of care and the only treatment able to change the bleeding phenotype in patients with haemophilia A.[1] Over the last decade, extended-half-life (EHL) replacement factors have been in development to address treatment burdens associated with regular prophylaxis infusions, such as poor adherence, and to maintain high factor VIII (FVIII) trough levels required to increase bleed protection, compared with standard-half-life replacement factors.[1] Several methods have been employed to extend the half-life of recombinant FVIII, including PEGylation[2,3] and Fc-fusion technology,[4] which have resulted in either increased protection from bleeding or effective prophylaxis regimens with longer intervals between doses, or both, compared with patients' previous standard-half-life treatment. The recently published third edition of World Federation of Haemophilia Guidelines for the Management of Haemophilia by Srivastava et al. report an updated, robust, evidence-based assessment of these advances in haemophilia treatment and management since the second edition, published in 2013,[1,5] that will no doubt be well-received by the haemophilia community. However, new evidence has come to light that may question Srivastava et al.'s statement asserting there are no significant differences in pharmacokinetic (PK) properties between EHL FVIII products,[1] although whether this evidence translates into clinical significance remains to be explored.

Two, recently published, prospective, head-to-head studies have shown significant differences between key, clinically relevant, PK parameters of different EHL FVIII products.[6,7] In 2019, Shah et al. reported a head-to-head comparison of the PK profiles of two EHL FVIII products, BAY 94-9027 (damoctocog alfa pegol; Jivi®, Bayer AG, Germany) and recombinant FVIII Fc fusion protein (rFVIIIFc; Elocta/Eloctate®; Biogen, Cambridge, MA, USA), in 18 patients with severe haemophilia A.[6] The single-dose, randomised, crossover study design allowed evaluation of PK parameters using the same assay in the same population of patients, thus enabling a direct intra-individual comparison of the two products. In this analysis, the authors observe a significant increase in geometric mean area under the curve ($P = .0001$), significant reductions in clearance ($P = .0001$), and a significantly longer geometric mean half-life after a BAY 94-9027 infusion compared with rFVIIIFc ($P < .05$, Table 1). Using popPK modelling, a longer time to different FVIII threshold levels (1, 3, 5 and 10 IU/dl) after a single infusion with BAY 94-9027 compared with rFVIIIFc was demonstrated.[6] This potentially enables longer intervals between doses, or higher FVIII levels for longer periods as predicted.

Another, similar, single-dose, randomised, crossover study by Solms et al. (2020), also reported significant differences in area under the curve, clearance and half-life between two EHL FVIII products (Table 1).[7] PK parameters of BAY 94-9027 and BAX 855 (rurioctocog alfa pegol; Adynovi®/Adynovate®; Takeda, Japan) were directly compared in 18 patients with severe haemophilia A, as well as a simulation of time to various FVIII thresholds using population PK modelling. The PK superiority of BAY 94-9027 was clearly observed in each reported parameter. The results of these two head-to-head studies of BAY 94-9027 versus rFVIIIFc, and versus BAX 855, demonstrate the consistently enhanced PK parameters with BAY 94-9027 compared with other EHL FVIII products. These data show clear, although minor, differences in PK parameters between the EHL FVIII products, however the clinical significance of these differences remains to be determined.

Conversely, and reflective of Srivastava et al.'s statement, PK profiles of rFVIIIFc and BAX 855 generated by the Web Accessible Population Pharmacokinetic Service-Hemo tool (WAPPS-Hemo.org) in adolescents with haemophilia A were not significantly different.[8] No significant differences were found with respect to half-life, area under the curve, clearance, time to FVIII thresholds 1, 3 and 5 IU/dl when patients switched from rFVIIIFc to BAX 855 prophylaxis. However, this study used population PK modelling to generate PK profiles with sparse sampling (four samples at different post-infusion timings for each product), and was not designed as a crossover study, so no comparisons were made in the opposite switching direction from BAX 855 to rFVIIIFc.[8]

Head-to-head studies overcome issues around interpatient variability, thus minimising the potential for confounding, and ensuring a valid, robust comparison of two products.[6,7] Results from intertrial or indirect comparisons of PK parameters can be misleading, potentially affected by many factors such as assay type, type of software used

TABLE 1 Summary of key PK parameters after a single infusion of EHL FVIII products obtained from head-to-head crossover studies in patients with severe haemophilia A[6,7]

	BAY 94-9027 versus rFVIIIFc, Shah et al.[6]				BAY 94-9027 versus BAX 855, Solms et al.[7]			
PK parameter	BAY 94-9027 (60 IU/kg)	rFVIIIFc (60 IU/kg)	Geometric LS mean ratio* (95% CI)	*P*	BAY 94-9027 (54.3 IU/kg)	BAX 855 (61.4 IU/kg)	(95% CI)	*P*
AUC, IU h/dl	3010 (38.3)	2400 (32.2)	1.26 (1.14–1.38)	.0001	NR	NR	NR	NR
$AUC_{norm,}$ kg/h/dl†	NR	NR	NR	NR	43.8 (44.0)	36.0 (40.1)	1.22 (1.11–1.33)	.0004
CL, dl/h/kg	.0200 (38.3)	.0250 (32.2)	.80 (.72–.87)	.0001	NR	NR	NR	NR
CL, dl/h	NR	NR	NR	NR	1.65 (46.4)	2.01 (42.0)	.82 (.75–.90)	.0004
$t_{½}$, h	16.3 (34.1)	15.2 (33.1)	1.07 (1.00–1.15)	<.05	17.0 (37.9)	16.0 (39.0)	1.06 (1.02–1.11)	.0064
Modelled time to 1 IU/dl FVIII threshold, h, median	117.0	104.0	NR	NR	120	104	NR	NR

Data are presented as geometric mean (%CV) unless stated otherwise.*Ratio of BAY 94-9027:rFVIIIFc or BAX 855. †AUC_{norm} was reported in the comparison of BAY 94-9027 and BAX 855 to account for potency differences. Potency-adjusted values are shown.*Abbreviations*: AUC, area under the curve; AUC_{norm}, area under the curve normalised for actual dose per body weight; CL, clearance; CV, coefficient of variation; EHL, extended half-life; FVIII, factor FVIII; NR, not reported; PK, pharmacokinetic; $t_{½}$, half-life.

in the compartmental approach, methods of quantification, among others, which may have an impact on the results.[7,9] Estimations of PK profiles determined using different methods should be compared with caution, as evidenced by studies reporting different half-life values for the same products.[8,9] The crossover study design used in the BAY 94-9027 head-to-head studies, which are currently the only studies of their kind in haemophilia, eliminate at least some pitfalls and inaccuracies.[6,7]

While the 1.4- to 1.6-fold differences in half-life observed between standard-half-life and EHL FVIII products are significant,[1,2,4,8] they are relatively small in comparison with those seen for factor IX equivalents.[1] However, it is important to note that half-life is not the only variable to consider when comparing the efficacy between two products. Besides half-life, other PK parameters such as increased area under the curve and reduced clearance, which contribute to time above FVIII threshold, could be of clinical significance, by translating into protection from bleeds for longer and thus reducing the risk of spontaneous bleeding into joints.[7] However, to our knowledge, this has so far not been studied in clinical trials and thus the clinical significance remains unknown.

While PK parameters are useful to predict clinical outcomes such as bleeding, we accept that PK is not the only measure of relative efficacy of EHL FVIII products. However, in the absence of prospective, longer term head-to-head efficacy and safety studies, head-to-head crossover PK studies remain the most impactful. The strength in the design of these studies of BAY 94-9027 with rFVIIIFc and BAX 855 offers a randomised, direct intra-individual comparison of PK parameters in the same patient population.[6,7] To date, these are the only published PK data from head-to-head studies, and due to their validity and reliability, the conclusions from these studies suggest there are, in fact, minor differences in PK properties between EHL FVIII products. Validation of these data with relevant clinical data from independent studies are welcomed. The half-lives of EHL FVIII products fall within a narrow range and the differences observed in head-to-head PK studies cannot yet readily be translated into clinical differences. Therefore, the question could still be raised, to which an answer remains elusive: are the statistically significant differences in PK parameters between EHL FVIII products clinically significant?

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DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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