Haemophilia
The Official Journal of the World Federation of Hemophilia,
European Association for Haemophilia and Allied Disorders and
the Hemostasis & Thrombosis Research Society

Haemophilia (2016), 1–12 DOI: 10.1111/hae.13013

REVIEW ARTICLE

The use of enhanced half-life coagulation factor concentrates in routine clinical practice: guidance from UKHCDO

P. COLLINS,* E. CHALMERS,† P. CHOWDARY,‡ D. KEELING,§ M. MATHIAS,¶ J. O'DONNELL,** K. J. PASI,†† S. RANGARAJAN‡‡ and A. THOMAS§§

**Arthur Bloom Haemophilia Centre, University Hospital of Wales, Cardiff; †Haemophilia Centre, Royal Hospital for Sick Children, Glasgow; ‡Katharine Dormandy Haemophilia Centre, Royal Free Hospital, London; §Haemophilia Centre, Churchill Hospital, Oxford; ¶Haemophilia Centre, Great Ormond Street Hospital, London, UK; **Haemophilia Centre, St. James Hospital , Dublin, Ireland; ††Haemophilia Centre, Royal London Hospital, London; ‡‡Haemophilia Centre, Basingstoke and North Hampshire Hospital, Basingstoke; and §§Haemophilia Centre, Royal Infirmary of Edinburgh, Edinburgh, UK*

Enhanced half-life factor VIII and IX products are being introduced into routine clinical practice. Published data report on clinical trials and there are limited data available on how to use these products in routine clinical practice. Many patients, for example, those with a past history of an inhibitor, have been excluded from clinical trials and there are limited data published on children. This guidance document is a consensus statement from the UK Haemophilia Centres Doctors' Organisation and aims to give pragmatic advice on the use of these products in routine practice.

Keywords: coagulation factor concentrates, enhanced half-life, pharmacokinetics, prophylaxis

Introduction

This guidance document aims to provide pragmatic advice on the use of enhanced half-life (EHL) factor VIIIs and IXs in routine clinical practice. The document is written from the perspective of the UK and may not be applicable in other countries. Reviews of clinical trials of EHL-FVIII/IXs have been published [1–5] and this document will not replicate those papers. This is a rapidly moving field and practice will evolve as more data become available and patients and the clinicians gain experience in the use of EHL-FVIII/IXs.

Overview of products, technologies and pharmacokinetic data

Three molecular strategies have been utilized to prolong the *in vivo* survival of FVIII and FIX coagulation factor concentrates (CFC). In these engineered CFCs, the native clotting factor glycoproteins have been modified via (i) addition of polyethylene glycol (PEG) [6–9]; (ii) fusion to recombinant human albumin [10]; or (iii) fusion to the Fc-region of human IgG [11,12].

PEGylation

PEGylation involves chemical coupling of PEG to the target protein, and has been used to extend circulatory survival for a number of approved human protein therapeutics. PEG chains vary in size (5–60 kDa) and can be attached using different chemical methodologies. Consequently, the number and size of PEG chains attached to the modified target protein, as well their specific attachment sites, can be engineered. As summarized in Tables 1 and 2, a number of PEGylated FVIII and FIX products have been studied in clinical trials. The biological mechanism(s) through which PEGylation inhibits *in vivo* clearance of FVIII and FIX has not been fully defined. However, PEGylation may be important in reducing susceptibility to *in vivo* proteolysis and inhibit LDL-receptor-related protein (LRP1) mediated clearance of FVIII [6,9].

Three PEGylated rFVIII products will be considered. Bax855 (Adynovate; Baxalta, Bannockburn, IL, USA) is a PEGylated form of full-length recombinant FVIII (rFVIII) expressed in Chinese Hamster Ovary (CHO)

Correspondence: Peter Collins, Haemophilia Centre University Hospital of Wales, Heath Park Cardiff CF14 4XN, UK.
Tel.: GRO-C fax GRO-C; e-mail: GRO-C GRO-C@wales.nhs.uk

Accepted after revision 12 May 2016

Table 1. Enhanced half-life factor VIII products: manufacturing characteristics and pharmacokinetics.

Product	Company	Cell line	Biochemical strategy	Age (years)	Subjects	Incremental recovery (IU dL^{-1})/(IU kg^{-1})	Half-life (h)	References
rFVIII-Fc	Sobi	HEK293H	B-domain-deleted rFVIII fused with human IgG_1 Fc domain	≥12	15	Mean (95% CI) 1.83 (1.6–2.1)	Mean (95% CI) 18.8 (14.3–24.5)	[17]
				≥12	28	Mean 2.2	Mean 19	[16]
				6–<12	31	Mean (95% CI) 2.44 (2.07–2.80)	Mean (95% CI) 14.9 (12–17.8)	[27]
				<6	23	Mean (95% CI) 1.92 (1.8–2.0)	Mean (95% CI) 12.7 (11.2–14.1)	
Bax 855	Baxalta	CHO	Full-length rFVIII with lysine PEGylation (20 kDa PEG ×2)	12–65	26	Mean (SD) 2.49 (0.69)	Mean (SD) 14.3 (3.8)	[15]
Bay 94-9027	Bayer Healthcare	BHK	B-domain-deleted rFVIII with site-specific PEGylation (single 60 kDa PEG)	≥18	14	Mean (range) 2.9 (2.1–4.1)	Mean (range) 18.2 (13.7–28.1)	[14]
N8-GP	Novo-Nordisk	CHO	B-domain-truncated rFVIII with site-specific PEGylation (single 40 kDa PEG)	≥18	26	Mean (SD) 2.4 (0.6)	Mean (SD) 19 (5.53)	[18]

Table 2. Enhanced half-life factor IX products: manufacturing characteristics and pharmacokinetics.

Product	Company	Cell line	Biochemical strategy	Age	Subjects	Incremental recovery (IU dL^{-1})/(IU kg^{-1})	Half-life (h)	References
N9-GP	Novo-Nordisk	CHO	rFIX with site-specific PEGylation (single 40 kDa PEG)	12–65	15	Mean (SD) 1.4 (0.4)	Mean (SD) 96 (42)	[21]
				12–65	30	Mean (CV) 2.0 (14.5)	Mean (CV) 93 (19.5)	[19]
				≥6–<12	13	Mean 1.6	Mean 76.3	[25]
				<6	12	Mean 1.5	Mean 69.6	
rFIX-Fc Alprolix	Sobi	HEK293H	rFIX fused with IgG_1 Fc	≥18	11	Mean (range) 0.87 (0.63–1.2)	Mean (range) 57.6 (47.9–67.2)	[24]
				≥12	22	Mean (95% CI) 0.92 (0.77–1.1)	Mean (95% CI) 82.1 (71.4–94.5)	[22]
				≥6–<12 Median (range) 8 (6–11)	13	Mean (95% CI) 0.72 (0.61–0.84)	Mean (95% CI) 70.3 (61.0–81.2)	[26]
				<6 Median (range) 2 (1–4)	11	Mean (95% CI) 0.59 (0.52–0.68)	Mean (95% CI) 66.5 (55.9–79.1)	
rFIX-FP	CSL Behring	CHO	rFIX fused with recombinant human albumin	12–65	28	Mean (SD) 1.4 (0.28)	Mean (SD) 91.6 (20.7)	[23]
				12–65	15	Mean 1.5	Mean 94.8	[20]
				≥6–<12	15	Mean (SD) 1.06 (0.239)	Mean (SD) 92.8 (19)	[36]
				<6	12	Mean (SD) 0.95 (0.20)	Mean (SD) 89.6 (11.2)	

cells (Advate), it has two 20 kDa PEG chains attached to specific lysine residues [9]. Bay 94-9027 (Bayer, Leverkusen, Germany) is a B-domain-deleted rFVIII molecule that contains a novel cysteine at residue 1804 [6]. Following expression in baby hamster kidney (BHK) cells, a single 60 kDa PEG group is added to this specific surface-exposed cysteine substitution. N8-GP (Novo Nordisk, Bagsværd, Denmark) contains a truncated B-domain of 21 amino acids and is expressed in CHO cells. Subsequently, a single branched 40 kDa PEG moiety is attached to an O-linked glycan within the residual truncated B-domain [8].

The PEGylated rFIX product (N9-GP) (Novo Nordisk) is synthesized in CHO cells prior to the attachment of a 40 kDa PEG to the FIX activation peptide by site-directed glycoPEGylation [7].

Fusion proteins

An alternative strategy to prolong *in vivo* survival is covalent fusion of other human proteins to FVIII/IX. Both human IgG and albumin have circulatory half-lives of approximately 3 weeks due to recycling through the neonatal Fc receptor (FcRn). Albumin and IgG molecules that undergo cellular endocytosis bind to the FcRn in a pH-dependent manner in the acidic conditions of the early endosome. Consequently, these FcRn-bound proteins are not targeted for lysosomal degradation, but are redirected to the cell membrane where they are released back into the plasma at neutral pH [13]. As summarized in Tables 1 and 2, a number of FVIII and FIX fusion products have been studied in clinical trials. rFVIIIFc (Eloctate;

Sobi, Stockholm, Sweden) is a recombinant fusion molecule expressed in human embryonic kidney (HEK293H) cells in which B-domain-deleted rFVIII is covalently linked to the Fc portion of human IgG_1 [12]. Similarly, rFIXFc (Alprolix; Biogen, Cambridge, MA, USA) is composed of rFIX expressed in HEK293J linked to the IgG_1 Fc domain [11]. In rFIX-FP, rFIX expressed in CHO cells has been covalently linked to recombinant human albumin (rFIX-FP; CSL Behring, Marburg, Germany) [10].

Overview of pharmacokinetics of enhanced half-life coagulation factor concentrate

In adults and adolescents (≥12 years), EHL-FVIII products have an average increase in half-life of about 1.5 times compared to the standard FVIII concentrates [14–18]. EHL-FIX products have a 3–5 fold increase in half-life compared to standard FIX concentrates [19–24]. These are average prolongations and there is wide inter-patient variability. As a consequence, the range of half-life with EHL-FVIII/IXs is larger than with the standard half-life products and it will not be appropriate to prescribe based on average half-life data for many patients. All published data on EHL-CFCs have excluded patients with a history of an inhibitor and it is possible that some of these patients will have shorter half-lives than those reported in clinical studies.

Published data for children (0–6 and 6–11 years) are limited, but the half-lives of EHL-FVIII/FIXs reported to date are shorter than in adolescents and adults (≥12 years). There is a progressive increase in half-life and incremental recovery (IR) across age bands and variability within each age band [25–27]. The change in half-life and IR with age must be taken into account when prescribing EHL-CFCs to children.

Prescribing enhanced half-life coagulation factor concentrates for previously untreated and minimally treated patients

Previously untreated patients

Although some EHL-CFC trials are enrolling previously untreated patients (PUPs), it will be some time before outcome data are available, especially for EHL-FIXs. PUP studies provide important safety, efficacy and pharmacokinetic data for this predominantly very young group of patients. Unpredictable side effects may be product- and/or age-specific. Unless a specific product has an unexpectedly high or low inhibitor incidence, it is unlikely that PUP studies will be adequately powered to detect differences in inhibitor rates compared to standard CFCs and other EHL-CFCs.

If the use of an EHL-CFC for a PUP is considered, entry into a PUP study should be offered. For logistical and eligibility reasons, it is likely that participation in PUP studies may not be practical in all cases. Consequently, there may be the need to consider the use of EHL-CFC products on a case-by-case basis out with a clinical trial before licencing. In such cases, careful discussion of the potential benefits and risks with the family is essential. The main perceived advantage of EHL-CFCs in children is the potential to reduce the frequency of dosing. However, from the limited data available to date, it appears that the benefit of EHL-FVIIIs products in reducing dosing frequency may be modest in boys under 2 years [27]. In contrast, the extension in half-life associated with EHL-FIX in young children with haemophilia B is more significant [25,26] and their use may avoid the need for port-a-cath insertion in some children.

Recommendation

> We suggest that previously untreated patients (PUPs) should be offered entry into a PUP study if available or, until further data are available, to commence treatment with a product licensed for PUPs.

Minimally treated patients

Previously treated patients are variably defined as having had >50–150 exposure days (EDs), although for licensing >150 EDs is used. Minimally treated patients (MTPs) are therefore defined as having had less than 50 or 150 ED. Prior to switching any MTP onto EHL-CFC treatment discussion of the potential benefits and risks with the patient and their family is required. Given that wide inter-individual variations in half-life have been reported, and that half-life and IR are less for children compared to adults, assessment of a limited PK study will be important prior to any EHL-CFC switch. A PK study will help to inform the decision about potential reduced dosing frequency and on whether to switch treatment [25–27].

In severe haemophilia, the highest risk of inhibitor development occurs during the first 50 EDs [28] and current paediatric PTP studies have excluded children with <50 EDs. Consequently, it seems reasonable to avoid switching to an EHL-CFC in patients with <50 EDs. In patients with a family history of inhibitor development, there may be an argument to remain on the same CFC product until >100–150 EDs. When any MTP is switched to a new product, patients should be screened for inhibitors prior to the first dose and after approximately 10 EDs after switching product.

Recommendations

In minimally treated severely affected patients, switching to an EHL-CFC can be considered after 50 EDs. In moderate/mild patients switching could be considered after fewer EDs. A limited half-life study should be performed.

Minimally treated patients should be tested for an inhibitor before and at approximately 10 EDs after switching product.

Switching to enhanced half-life coagulation factor concentrates

Clinical considerations when switching to EHL-CFCs have been reviewed [1–5,25,26].

Initial clinical consultation

If a switch to an EHL-CFC is being considered, an initial consultation should be held to discuss opportunities, expectations and possible adverse reactions. Some individuals may have no increase in half-life when switching to an EHL-FVIII, while other patients will have an above average increase. It is important that patients are aware of these variations and that EHL-FVIII may not allow a reduction in infusion frequency in all cases.

The individual's bleed pattern and planned activity should be reviewed. The balance between activity, frequency of infusions and cost of treatment should be discussed. Discussions will differ markedly for EHL-FVIIIs and EHL-FIXs and continuing with standard half-life CFCs may represent the best option for some individuals.

The importance of establishing individualized pharmacokinetic data should be explained [2,3]. The value of maintaining an accurate record of infusions and bleeds, for example, using Haemtrack (https://apps.mdsas.nhs.uk/haemtrack), after a change in treatment regimen should be emphasised.

Risk of inhibitor development

Available data suggest that there is a low risk of inhibitor formation after a PTP switches to an EHL-FVIII/FIX. However, there are no data for patients with a past history of an inhibitor. All patients should have an inhibitor test before switching and at about 10 EDs and 3 months after switching and then at least every 6 months or if clinically indicated [29]. Centres may wish to test more frequently in patients with a past history of an inhibitor.

Assessment of individual pharmacokinetics at the time of switching

When switching to an EHL-CFC, pharmacokinetic data should be obtained so that the individual's response to the agent is known [2,3]. Pharmacokinetic information is especially important if a patient has a past history of an inhibitor. Centres may wish to perform a limited pharmacokinetic assessment on the patient's current product for comparison, however, this information should not be used to predict EHL-CFC pharmacokinetics on an individual basis. There are a number of options:

1. A full pharmacokinetic analysis. This is demanding, labour intensive and may not be feasible for many patients [30].
2. Population pharmacokinetic and Bayesian analysis using reduced sampling. This requires that population pharmacokinetic models are made freely available by manufacturers for each agent.
3. If the above two options are not possible, we suggest a test dose (50 μ kg^{-1} children, 25–30 μ kg^{-1} adults) of EHL-CFC be given and factor levels measured to define individual pharmacokinetic information for optimization of treatment for prophylaxis and bleeding episodes. Centres may consider collaborating with WAPPS-Hemo (https://plus.mcmaster.ca.wapps-hemo/). The follow time points are suggested but may be modified for young children:

   EHL-FVIII: preinfusion, 15 min post dose and approximately 6, 24, 48 and 72 h postinfusion. Additional optional levels at 96 and 168 h may be performed in some patients.
   EHL-FIX: preinfusion, 15 min postinfusion and approximately 24, 72, 120 and 168 h postinfusion. Additional optional levels at 240 and 336 h may be performed in some patients.

Consultation to implement change of regimen

After the individual pharmacokinetic data have been defined, a further consultation should take place to optimize the new EHL-CFC regimen. Prophylactic dose and interval should be agreed. Regimens for the treatment of bleeding episodes should be agreed based on the individual incremental recovery (IR) and half-life and the importance of accurate records reiterated. Events necessitating contact with the haemophilia centre should be agreed.

Follow-up after switch to enhanced half-life coagulation factor concentrate

Close follow-up of the new treatment regimen is important. An inhibitor screen should be performed

after approximately 10 EDs, or earlier if clinically indicated. Patients should be clinically reviewed within 4 weeks after switching, this could be by telephone. A clinical review should be scheduled for about 3 months after switching and an inhibitor screen performed. IR and trough FVIII/IX levels should be measured around that time. If one EHL-CFC does not provide adequate clinical outcomes after tailoring dose and frequency, an alternative agent may be tried or the patient could switch back to standard half-life treatment.

The regimen should be adjusted over time based on the pattern of break-through bleeds and measured levels. If break through bleeds occur, increasing the frequency of infusions, while maintaining the same the total dose of CFC, will result in higher trough levels. If bleeds occur in association with planned activity, the timing of peak levels should be reviewed. In patients who experience no bleeding episodes, a reduction in dose or frequency could be considered and measurement of trough FVIII/IX levels may be useful.

Recommendations

An initial consultation should be held to realistically consider potential regimens with an EHL-CFC. Patients should be made aware that EHL-FVIIIs may not allow a reduction in infusion frequency for all individuals.

A test dose of EHL-CFC should be given and pharmacokinetic data derived to define an individualised incremental recovery and half-life so that the treatment regimen can be optimized.

We suggest that patients with a past history of an inhibitor that has been tolerised within the last year should not switch CFC.

After switching to an EHL-CFC, individuals should be followed up 4 weekly, in person or by other medium, for 3 months to assess the pattern of bleeds. Trough levels should be measured. An inhibitor screen should be performed at about 10 EDs and 3 months after switching or if clinically indicated.

All patients should be assessed for regimen efficacy based on annualised bleed rate, adherence, convenience, joint score and annualised treatment cost after 1 year on an EHL-CFC.

Management of bleeding episodes with enhanced half-life coagulation factor concentrates

At the time of switching to an EHL-CFC, a consultation should take place to agree a protocol for the treatment of bleeding episodes. Until individuals have gained experience in treating bleeds with an EHL-CFC, they should be encouraged to contact the haemophilia centre regularly for advice to optimize bleed management.

The effectiveness of the EHL-CFCs to arrest bleeding is likely to be determined mainly by peak plasma levels. The initial treatment dose should take into account the time of the last infusion of EHL-CFC and the estimated factor VIII/IX. This is especially relevant for EHL-FIX. The expected preinfusion FVIII/FIX level can be estimated based upon the patient's individual pharmacokinetic profile.

The dose of treatment will depend on the type and severity of the bleed, the expected incremental recovery (IR) and the target FVIII/IX level. A single infusion appears to be effective for most bleeds in both haemophilia A and B (Table 3), although severe bleeds will require therapeutic FVIII/IX levels to be maintained for an extended period. Patients should be encouraged to contact their Haemophilia Centre if there is no resolution within 24–48 h, or earlier if there is concern, to discuss further management. Consideration should be given to clinical review at the Haemophilia Centre, measurement of FVIII/IX levels and inhibitors testing prior to the third dose because failure to respond to two infusions may suggest lack of efficacy, a more severe bleed, unexpectedly low FVIII/IX levels or inhibitor development.

If a patient consistently requires more than two infusions for bleed resolution, the patient should be reviewed and pre- and post-FVIII/IX levels measured to ensure that the efficacy of the EHL-CFC is adequate and the treatment use appropriate. Switching to an alternative EHL-CFC or a standard half-life CFC should be considered if efficacy is unexpectedly poor.

Management of bleeding episodes with enhanced half-life coagulation factor concentrates in children

Although the principles of bleed management outlined above also apply to children, there are only limited published data for children <12 years. In addition, the half-life of FVIII-Fc is shorter and IR lower in children <6 and 6–<12 years than adult and adolescents [27]. Data on pharmacokinetics in young children with other EHL-FVIIIs are awaited. Consequently, in some cases, an EHL-CFC FVIII may need to be infused more often than once daily. Similarly, IR and half-life

Table 3. Treatment of bleeding episodes with enhanced half-life coagulation factor concentrates.

Product	Age (years)	Average units kg^{-1} for treatment of bleeds	% treated with one infusion	% treated with one or two infusions	References
Factor VIII					
rFVIII-Fc	≥12	27.35	87.3	97.8	[16]
	<12	49.7	81.4	93	[27]
N8-GP	≥12	ND	ND	95.3	[48]
Bax 855	12–65	29.0	85.5	95.9	[15]
Bay 94-9027	ND	ND	ND	ND	
Factor IX					
Fc Fusion	≥12	46	90.4	97.3	[22]
FIX	<12	63.5	75	91.7	[26]
N9-GP	12–65	40	84.1	98.6	[19]
	0–<12	43	85.7	97.6	[25]
rIX-FP	12–65	62	95.3	100	[20]
	12–65	35–50	93.6	98.6	[49]
	<12	ND	ND	97	[50]

were lower for children aged 0–11 years than those aged ≥12 years for rFIX-Fc and N9-GP [25,26]. This should be taken into account when advising on an initial dose to treat a bleed and the timing of subsequent doses.

Parents should be encouraged to maintain close contact with their Haemophilia Centre for advice on the management of bleeds. Severe bleeds may require two infusions of EHL-FVIII on the first day. Clinical review and measurement of factor levels may be beneficial if bleeds do not resolve after two infusions to assess the severity of the bleed and determine the optimal treatment. Inhibitor testing may also be required.

Recommendations

Treatment of bleeding episodes in patients on EHL-CFCs should be based on the severity of the bleed, the individual's incremental recovery, half-life and age.

The first infusion should raise the FVIII/IX to a level appropriate for the type of bleed, taking into account the time and dose of the previous infusion.

If bleeds do not resolve with two infusions, patients should discuss further treatment with their Haemophilia Centre. Clinical review, measurement of FVIII/IX levels and inhibitor testing may be required to optimise management.

Management of prophylaxis with EHL-CFCs

The current paradigm for prophylactic therapy with standard half-life CFCs is for dose and interval to be adjusted in response to bleeding events and, in some cases, to maintain a target trough level. The optimum trough level for an individual varies and can only be established by clinical observation. Adequate trough levels on standard half-life products may not be appropriate for EHL-CFCs, since the latter will be associated with longer times at low levels, especially for EHL-FIX, [31,32]. Tailoring dose and frequency of an EHL-CFC to an individuals' pattern of bleeding, life style and pharmacokinetics will be important after switching to these agents [2]. Haemophilia centres should be made aware of all bleeds on a new agent to assess response to the new prophylactic regimen.

Prophylactic use with all EHL-FVIII/FIXs markedly reduces annualized bleeding rates (ABRs) compared to on-demand treatment and an infusion every 3rd or 4th day in haemophilia A or weekly in haemophilia B can achieve low or zero ABRs in the majority of adults/adolescents (Tables 4 and 5). In all studies where data were reported, there was a range of responses. Importantly, a proportion of patients in some studies reported ABRs that were unacceptably high compared to standard UK care, especially in unselected patients taking once weekly EHL-FVIII regimens [16,33]. Less frequent regimens (once a week for haemophilia A and every 10–14 days for haemophilia B) are less cost-effective because a higher total dose of CFC is required to maintain a target trough level. However, these regimens may be feasible in a subgroup of patients with low ABRs on standard regimens. It is not possible to compare prophylaxis efficacy between EHL-CFCs because trial design and reporting differs (for reviews see [1,3–5]).

The potential benefits and drawbacks of EHL-CFCs for prophylactic therapy have been reviewed [1–5]. The main advantage of EHL-CFCs is the need for fewer venipunctures while maintaining acceptable ABR and trough levels. However, the lower the frequency of infusions, the fewer peaks an individual will have and the longer the time spent at FVIII/IX levels close to the trough [3,31,34]. Whether this will influence outcomes is currently unknown. The ABR of an individual should not be allowed to increase following a switch to EHL-CFCs and long term and regular follow-up of joint outcome measures would be advised.

Prophylaxis in children

A study in young children (0–6 and 6–11 years) investigating rFVIII-Fc reported a shorter half-life than in adolescents and adults (≥12 years) (Table 1) [27]. Data on other EHL-FVIIIs are awaited. Therefore, paediatric prophylactic regimens with EHL-FVIII will not necessarily conform to those for adults. In young children, because of the shorter half-life and the

Table 4. Prophylactic treatment with enhanced half-life factor VIII concentrates.

Product	Age	Regimen	Number of subjects	ABR	References
Bax 855	12–65	45 IU kg^{-1} twice weekly	120	Median (IQR) 1.9 (0–2)	[15]
N8GP	≥12	50 IU kg^{-1} every 4 days	175	Median 1.3	[48]
FVIII-Fc	≥12	25 IU kg^{-1} day 1 and 50 IU kg^{-1} day 4	118	Mean (95% CI) 2.9 (2.3–3.7)	[16]
		65 IU kg^{-1} weekly	24	Mean (95% CI) 8.9 (5.5–14.5)	
	<6	25 IU kg^{-1} day 1 and 50 IU kg^{-1} day 4	36	Median (IQR) 0 (0–4)	[27]
	6–12		35	Median (IQR) 2 (0–4)	
Bay 94-9027	12–65	25 IU kg^{-1} twice weekly for 10 weeks: >1 bleed changed to 30–40 IU kg^{-1} twice weekly	13	4.1	[36]
		25 IU kg^{-1} twice weekly for 10 weeks: ≤1 changed to 45 IU kg^{-1} every 5 days	43	1.9	
		25 IU kg^{-1} twice weekly for 10 weeks: changed to 60 IU kg^{-1} once weekly	43	Median (IQR) 3.9 (0–6.5) (all patients) 11 dropped out with median ABR 16.9 32 completed ABR 0.96 (0–4.3)	

Table 5. Prophylactic treatment with enhanced half-life factor IX concentrates.

Product	Age (years)	Regimen	Number	ABR	References
rFIX-FC	12–65	50 IU kg^{-1} once weekly: dose adjusted to trough 1–3 and to prevent bleeds	61	Mean (95% CI) 3.12 (2.46–3.95)	[22]
		100 IU kg^{-1} every 10 days: interval adjusted to trough 1–3 and to prevent bleeds	26	Mean (95% CI) 2.40 (1.67–3.47)	
	<6 Median (range) 2 (1–4)	50–60 IU kg^{-1} once weekly: adjusted up to 100 IU kg^{-1} and between once and twice weekly	15	Median (IQR) 1.1 (0.0–2.9)	[26]
	6–<12 Median (range) 8 (6–11)		15	Median (IQR) 2.1 (0.0–4.2)	
N9-GP	12–65	10 U kg^{-1} once weekly	30	Median IQR 2.9 (1.0–6.0)	[19]
	12–65	40 U kg^{-1} once weekly	29	Median (IQR) 1.0 (0.0–4.0)	
	<6	40 IU kg^{-1} once weekly	12	Med (range) 0 (0–3)	[25]
	6–<12	40 IU kg^{-1} once weekly	13	Med (range) 2 (0–6.5)	
FIX-FP	12–65	30 IU kg^{-1} adjusted to bleeding pattern	13	Mean 4.35	[20]
	12–65	40 IU kg^{-1} weekly	40	Median (IQR) 0 (0–1.87)	[49]
		75 IU kg^{-1} every 14 days	21	1.08 (0–2.7)	
	<12	46 IU kg^{-1} weekly	27	Med (IQR) 0 (0–0.91)	[50]

recommendation to aim for zero bleeds [35], it is likely that the time between infusions will need to be shorter and once weekly regimens are unlikely to be adequate. Break-through bleeds are more likely to be prevented by increasing the frequency of infusions while using the same total dose rather than increasing the dose.

A progressive improvement in FVIII half-life is likely to occur with age and so, depending on the physical activity, it may be possible to reduce the dose or frequency as children become older.

Enhanced half-life-factor IX paediatric prophylaxis studies have been presented as abstracts and for both rFIX-Fc and N9-GP, the half-life was shorter for 1–6 and 6–11 year olds compared to patients ≥12 years [25,26]. The half-life of rIX-FP was similar for children <12 years compared to adults [36]. Low median ABRs were reported for all products, but some boys had ABRs that would be considered too high for UK standard practice, especially in the 6–12 year olds [25,26]. Based on these limited data, it is likely that young children with haemophilia B will need to be treated at least once a week, and some more often, to provide adequate protection from bleeds.

Potential strategies for prophylaxis

There are a number of options for using EHL-CFCs for prophylaxis.

1. Infusions at reduced frequency (every 3rd or 4th day or twice a week for FVIII and once weekly for FIX) aiming for a standard trough level. In selected subgroups, infusions at lower frequency (once weekly for FVIII and every 10–14 days for FIX) may be feasible but these regimens will require more CFC to maintain a target trough level. Maintaining a measurable trough with once weekly EHL-FVIII is unlikely to be feasible for the majority of patients.
2. Infusions at traditional frequency (every 2 days for FVIII and every 3rd or 4th day for FIX) to achieve a higher trough level.
3. Hybrid regimens that use increased amounts of EHL-CFC to improve both trough levels and reduce frequencies.

For any target trough level, exponentially more CFC will be required as the time between infusions increases and this will dramatically impact on the cost effectiveness of the regimen.

When considering the most appropriate CFC and dosing regimen for an individual, it is important to understand their circumstances and pattern of bleeds. Consequently, EHL-CFCs used at decreased frequency may not be the best option for all patients. An individual who wishes to participate in regular active sport may not have adequate prophylactic cover if they receive twice weekly infusions of EHL-FVIII or once weekly EHL-FIX because of insufficient FVIII/FIX at the time of all activity. Higher levels and more frequent peaks may also be needed for patients with target joints. These patients, or those who have a less than average half-life prolongation, may elect to continue on standard half-life products at high frequency. Individuals who participate in sport only at the weekend may have adequate prophylaxis with appropriately timed twice weekly EHL-FVIII or weekly EHL-FIX. People who have a more sedentary lifestyle may be successfully treated with EHL-FVIII once weekly or EHL-FIX every 10–14 days.

Factor VIII prophylaxis

In most adults, an appropriate initial prophylaxis regimen for haemophilia A with an EHL-CFC will be every 3rd or 4th day or twice a week depending on the individual half-life. If twice weekly regimens are used, then the dose before the 4-day interval will need to be more than double the dose before the 3-day interval to maintain the same trough level. More frequent dosing may be needed for young children. The regimen should ensure that peak levels coincide with times of predictable activity. The initial target trough level should be similar to that obtained for the patient with standard half-life FVIII.

Factor IX prophylaxis

In most cases, an appropriate initial prophylaxis regimen for haemophilia B will be once weekly. Tailoring based on observed bleed pattern and measured levels may allow some adult patients to achieve adequate bleed prevention with infusions every 10–14 days. However, this is a less cost-effective way to use these products because a higher total dose is required to maintain a target trough level. Infusions more frequent than once a week may be needed in young children. As with EHL-FVIII, break-through bleeds are more likely to be prevented by increasing the frequency, while maintaining the same the total dose, rather than increasing the dose.

Recommendations

Prophylactic regimens with EHL-CFCs should be tailored based upon individual pharmacokinetics and personal circumstances. Accurate records of infusions and bleeds are important for optimising treatment.

In some patients continuing with standard half-life products may be the preferred option.

Typical initial regimens with EHL-CFCs in adults will be every 3rd or 4th day or twice a week depending on individual half-life in haemophilia A and once weekly in haemophilia B.

In a subgroup of adult patients, prophylaxis modification after switching may be possible based on bleed pattern such that treatment frequency can be further reduced to every 5 days or once weekly for haemophilia A and every 10–14 days for haemophilia B. These are less cost-effective regimens because a high total dose is required to maintain a target trough level.

The target ABR in children is zero. Due to shorter half-lives in this age group, it is unlikely that regimens less frequent than every 3rd or 4th day for haemophilia A and once weekly for haemophilia B will provide adequate prophylaxis. In addition, more frequent infusions may be required, especially for children <6 years.

After switching to an EHL-CFC, prophylactic regimens must be closely monitored (initially at least monthly) and if the ABR increases the regimen should be reviewed and adjusted if appropriate or the patient switched back to a standard half-life product.

Surgery in patients with haemophilia A and B

Haemophilia A

To date, data for rFVIII-Fc and N8-GP have been reported for prevention of bleeding in minor and major surgeries. Both products were reported to have good efficacy, although the number of procedures reported remains low [16,37]. Data on other EHL-FVIII products are awaited.

Haemophilia B

Enhanced half-life-factor IXs have been used for prevention of bleeding in relation to minor and major surgeries. Treatment regimens took into account the

current WFH guidelines but were predominantly at the discretion of local investigators. All EHL-FIXs were found to be efficacious for minor and major procedures, including joint replacement. Nevertheless, the number of procedures reported remains low. Once-daily dosing was possible from day 1 for major surgery and one to two doses were adequate for most minor procedures. There were no reports of venous or arterial thromboembolism [38–40].

Potential approach to surgery. Preoperatively, the clinicians should determine the target FVIII/IX level at the time of surgery, the acceptable postoperative trough level and the length of time this level should be maintained. For major surgery, an adequate level will need to be maintained until wound healing has occurred. For minor surgery, one infusion of EHL-FIX and one or two infusions of EHL-FVIII may be sufficient. There are no data on the use of continuous infusion for EHL-FVIII/IXs.

- An initial bolus infusion should be given to raise FVIII/IX to the predetermined level based on the known IR for the patient. Pre and post FVIII/IX levels should be measured to ensure that an adequate peak level is achieved.
- For major surgery, a fall off level should be measured postoperatively and on the following day to determine the time and dose of the next infusion based on clinical response and the minimum acceptable level.
- For haemophilia A, a second infusion on the day of surgery may be required. Infusions at least daily are likely to be required initially to maintain an adequate trough level following major surgery.
- For haemophilia B, once-daily dosing is likely to be feasible from day 1 and less frequently infusions may be possible if measured FIX levels are adequate.

Monitoring enhanced half-life coagulation factor concentrates

EHL-CFCs have an assigned labelled potency and clinical laboratories need to be able to measure a comparable activity in postinfusion patient samples. Currently, the European Pharmacopoeia defines the chromogenic FVIII assay for potency labelling of FVIII products and the one-stage clotting assay for FIX products. The ISTH SSC has recently made recommendations for potency labelling [41] and the European Medicines Agency (EMA) held a workshop to discuss the issues (report available at http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/events/2013/09/event_detail_000777.jsp&mid=WC0b01ac058004d5c3) [42]. There is concern regarding how clinical laboratories can achieve a comparable activity measurement on postinfusion samples and the implications of this on patient's safety.

For EHL-FVIIIs, a chromogenic assay will normally give a result consistent with the labelled potency. Using an automated chromogenic assay for postinfusion, FVIII estimation may be the simplest solution, provided the particular chromogenic assay has been validated for use with the product in question. An alternative is to use a one-stage APTT-based coagulation assay that has been shown to give a comparable result when measuring against a human plasma standard. For rFVIII-Fc, it is stated that many APTT reagents may give acceptable results [43], although individual reagent data were not given; for others (e.g. PEGylated rFVIII), only a few specific reagents may be acceptable [44] (Table 6). Laboratories cannot be expected to use specific APTT reagents for specific products and so, if their standard reagent does not give comparable results with a human plasma standard, then an alternative is to use a product-specific standard spiked into FVIII-deficient plasma. We recommend against using an assay known to give discrepant values and multiplying the result by a correction factor.

Table 6. Monitoring enhanced half-life coagulation factors.

Product	Study	Reagents stated to be acceptable*	Unacceptable reagents	Notes
rFVIII-Fc	[43]			A field study states that a specific standard is not needed but individual reagent data are not given
N8GP		ND	ND	
Bay 94-9027	[44]	SynthAFax (Werfen), Actin (Siemens), STA-Cephascreen (Stago)	HemosIL APTT-SP (Werfen), STA PTT (Stago)	
Bax 955		ND	ND	
rFIX-Fc	[45]	STA-PTT (Stago), Actin (Siemens), Actin – FSL (Siemens), SynthAFax (Werfen), HemosIL SynthaSil (Werfen), Triniclot Auto-APTT (Stago)	STA CK Prest (Stago)	
N9GP	[46]	SynthaFax (Werfen)		
Albumin-FIX		ND	ND	

*UKHCDO cannot endorse these agents as suitable on the basis of limited data from studies to date and they are given as a guide only.

For EHL-FIXs, the same principles apply but chromogenic assays are less widely available. For rFIX-Fc and N9-GP, it is stated that some APTT reagents give acceptable results [45,46] but this is not the case for all reagents (for example, rFIX-Fc with the one reagent using kaolin as the activator). For EHL-FIXs, when the standard laboratory reagent used with a human plasma standard does not give a comparable result to the labelled potency, a product-specific standard will be necessary for assay of postinfusion patient samples.

Recommendations

Laboratories should use an assay that has been validated for use with the specific EHL-CFC. This may be a chromogenic assay, a one stage assay with a method shown to give appropriate results or a one stage assay with an appropriate product specific standard.

Laboratories should not use an assay known to give discrepant values and multiply the result by a correction factor.

Pharmacovigilance for enhanced half-life coagulation factor concentrates

For treatment of people with bleeding disorders in the UK, there is a well-established mechanism for reporting suspected adverse reactions through the National Haemophilia Database (NHD) coordinated by the UKHCDO. The European Haemophilia Safety Surveillance (EUHASS) collaboration, a pharmacovigilance programme to monitor the safety of treatments for people with inherited bleeding disorders in Europe, has also been in operation since 2008.

Safety concerns with EHL-CFCs may be a class effect, common to all the products, or an effect unique to the particular product. Class effects include: inhibitor formation and hypersensitivity. Thromboembolic events including cardiovascular events, poor efficacy and potential for off-label use are examples of important potential risks.

Important missing information may include safety in pregnancy and lactation and patients not extensively studied in trials including paediatric patients and those with a past history of an inhibitor. Particular additional concerns with the EHL-CFCs include accurate monitoring of factor levels, prescribing errors, altered immunogenic potential and long-term safety. This last is particularly relevant for PEGylated products because the effect of PEG accumulation over time in humans is not known. Vacuolation of renal tubules and ependymal cells has been reported in animals in association with repeated long-term exposure (0.4 $\mu g\ kg^{-1}\ month^{-1}$) to proteins PEGylated with molecules >40 kDa and the vacuoles were shown to contain PEG [47].

Information on adverse events should be reported to NHD (in the UK), the manufacturer and if appropriate EUHASS. For EHL-CFCs, this should include inhibitor formation, infection, death, allergy, malignancy, thrombosis and poor efficacy. Additional information that should be reported includes: off-label prescribing, prescribing errors and difficulties with monitoring. For PEGylated products, evidence of deterioration in renal function or neurological problems should be reported.

Disclaimer

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Disclosures

Peter Collins: Consultant for Sobi, CSL, Bayer, Novonordisk and Baxalta. Sponsorship to attend meetings: Baxalta, Novonordisk, CSL and Bayer. Research support from CSL. Elizabeth Chalmers: has received fees for consulting for Beorhinger Inglehiem, and Novartis, fees for speaking from Sobi and reimbursement for attending a symposium from Novo Nordisk. Pratima Chowdary: Honoraria Bayer, Baxter, Biogen Idec, CSL, Novonordisk, Pfizer, Sobi. Advisory boards Baxter, Biogen Idec, CSL, Novonordisk, Pfizer, Sobi. Research funding CSL, Novonordisk and Pfizer. David Keeling: Paid attendance at Advisory Board Sobi, Baxalta and Pfizer. Meeting attendance Bayer and CSL. Mary Mathias: Speaker fees from Novonordisk and Bayer. Meeting support from Bayer and CSL. James O'Donnell: Consultant for Baxalta, Bayer, Novonordisk, Boeringher Ingleheim, Leo Pharma, Octapharma, Daiichi Sankyo. Research support for Baxalta, Bayer, Pfizer and Novonordisk. K John Pasi: Research support from Octapharma. Consultancy Biogen, Sobi, Octapharma, Genzyme and Pfizer. Honoraria for education from Novonordisk. Savita Rangarajan: No conflicts. Angela Thomas: No conflicts.

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