Changing paradigm of prophylaxis with longer acting factor concentrates

M. CARCAO
Division of Haematology/Oncology, Department of Pediatrics, Child Health Evaluative Sciences, Research Institute, The Hospital for Sick Children, Toronto, ON, Canada

Summary. Beginning in the 1960s the care of persons with haemophilia began to improve dramatically through a series of transformative improvements in care: development of lyophilized factor concentrates, home care programmes, prophylaxis and (due to the tragedy of HIV/hepatitis) the development of virally safer plasma-derived and recombinant factor concentrates. Prophylaxis, if commenced early and given in sufficient dose/frequency has been shown to allow persons with haemophilia to maintain excellent joints and lead normal lives. Yet the relatively short half-lives of factor (F) VIII and IX concentrates leads to the need for frequent venous access. This remains a significant burden for patients with haemophilia on prophylaxis causing in many cases reduced patient adherence to prophylaxis and negative longterm outcomes. The last 5 years have witnessed a flourish of new bioengineered longer acting FVIII and IX concentrates manufactured using different technologies (pegylation or fusion to Fc/albumin). These products (especially the longer acting FIX concentrates) are likely to have profound implications on prophylaxis. With these longer acting factor concentrates prophylaxis regimens will almost certainly change. This will involve changes in what trough levels are targeted and how frequently factor is administered. It is hoped that these changes may improve patients’ adherence to prophylaxis and their quality of life. These long-acting factor concentrates will undoubtedly have cost repercussions and will raise important questions regarding how decisions about choosing one longer acting concentrate over another, and whether these products are interchangeable, are made. This article will review what changes may ensue with the advent of these new longer acting factor concentrates.

Keywords: Fc or albumin fusion technology, haemophilia, longer acting factor concentrates, pegylation, prophylaxis

Introduction
Prior to the 1960s, there was virtually no therapy available for persons with haemophilia. All this changed in the early 1960s with the discovery of cryoprecipitate [1]. In the late 1960s and into the 1970s, freeze-dried plasma-derived (pd) factor concentrates were developed, allowing patients to treat themselves when needed (home care). In the early to mid-1980s, it was recognized that these pd factor concentrates were contaminated with HIV, thus setting a tremendous impetus towards improved pathogen screening, better viral inactivation techniques, and the development of recombinant factor concentrates [2]. The first recombinant (r) FVIII was licensed in the early 1990s and the first rFIX in 1997 [3]. Despite these remarkable advances no improvements have, until now, been made to the pharmacokinetic properties of factor concentrates. Consequently, currently available FVIII concentrates, whether plasma-derived or recombinant, have virtually indistinguishable pharmacokinetics; the same is true for FIX concentrates, with the only exception being that rFIX shows a lower recovery than pdFIX concentrates [4]. The last 5 years have witnessed a flourish of new bioengineered longer acting factor concentrates, which are likely to be licensed within 1–2 years and which may have profound implications on prophylaxis. This article will review where prophylaxis currently is and what changes may ensue with the advent of these new longer acting factor concentrates.
Where prophylaxis is: as of 2014

The development of factor concentrates allowed persons with haemophilia to be infused on a regular basis to prevent bleeds (prophylaxis), based on the hypothesis that by prophylactically replacing FVIII or FIX concentrates on a regular basis, the phenotype of severe haemophilia could be changed to that of moderate haemophilia. The earliest pioneers of prophylaxis were Professor Inge-Marie Nilsson and colleagues in Malmö, Sweden [5]. They demonstrated that when prophylaxis was started early and administered regularly (primary prophylaxis), patients with severe haemophilia had significantly reduced bleeding, maintained excellent joints and were able to lead normal lives. The superiority of prophylaxis over on-demand therapy (the administration of factor only when patients experience a bleed) was subsequently demonstrated by many cohort studies in the 1990s and 2000s [6–8] and finally, in a landmark randomized trial published by Manco-Johnson and colleagues in 2007 [9].

Prophylaxis is defined as the administration of factor on a regular basis to prevent bleeding and to preserve short- and long-term health [10]. Many investigators have proposed a minimum of once weekly infusions for 45 weeks/year as the minimum frequency and duration of regular infusions that would constitute continuous prophylaxis [11]. Prophylaxis has been further subdivided according to when it is commenced and according to its intensity (dose/frequency). For definitions of primary, secondary and tertiary prophylaxis please refer to a recent paper by the World Federation of Hemophilia [11]. The term ‘full-dose prophylaxis’ has been applied to the administration of high doses of factor 25–40 international units (IU) kg⁻¹ every other day for haemophilia A, and twice/week for haemophilia B. Intermediate- and low-dose prophylaxis refer to regimens using lower doses and/or less frequent administration of factor.

Much has been learned about prophylaxis using currently available factor concentrates. The earlier prophylaxis is commenced, the better the long-term results [12]. Consequently, primary prophylaxis is now considered optimal care for patients with severe haemophilia. When managing patients on prophylaxis many clinicians aim to achieve factor trough levels of >1%. In most, but not all patients, such a level is known to be effective in preventing bleeding. Yet some patients seldom bleed despite having levels of <1% while others (especially more physically active patients) need higher trough levels, attesting to the heterogeneity of the disease and potentially the need to individualize prophylaxis [13,14].

The biggest disadvantage of currently available factor concentrates relates to their relatively short half-lives, which results in the need for frequent infusions of factor. FVIII concentrates have half-lives in the range of 8–12 h but with much variability (6–24 h) [15], while FIX concentrates have half-lives in the range of 18–24 h [16]. Between persons there is significant variability in the pharmacokinetic handling of factor. In the case of FVIII much of this variability is related to a person’s endogenous clearance of VWF, which to a degree correlates with a person’s VWF levels, blood group, and age [17–20]. Less is known about what contributes to variability in the pharmacokinetic handling of FIX. A recent paper suggests that when FIX is infused, much of it goes into the extravascular tissue [21]. In contrast, the amount of FVIII that goes extravascular is negligible.

The need for frequent, inconvenient and painful infusions with currently available factor may lead to avoidance or delay in starting prophylaxis or, if a patient is already on prophylaxis, to missed doses, which immediately puts them at risk of bleeding. Many studies have shown that adherence to prophylaxis is far from ideal [22–24]. All of these issues are worse in very young children where peripheral venous access is, in the best of cases, difficult and in the worst, impossible.

The need for frequent infusions with currently available concentrates also leads to a substantial need for central venous access devices (CVADs; mainly port-a-caths). One study showed that 82% of children ≤5 years of age with severe haemophilia A on full-dose prophylaxis required a CVAD [25]. CVADs, although tremendously helpful, are associated with a substantial rate of mechanical failure, infections and thrombosis [26]. As such, many clinicians and investigators have adopted escalating-dose prophylaxis in which young children are commenced on once weekly infusions, escalated to twice weekly infusions and eventually (in the case of severe haemophilia A), to every other day or full-dose prophylaxis. One approach escalates all patients regardless of whether they are bleeding, while an alternative approach tailors prophylaxis to bleeding and only escalates those patients experiencing unacceptable bleeding [25,27]. Tailoring prophylaxis is predicated on the observation that bleeding frequency varies significantly among patients with severe haemophilia A [28,29]. Both approaches allow patients and families time to psychologically accept peripheral venipunctures and have been demonstrated to reduce the number of CVADs required. With these approaches, recent experience suggests that about 30% of young children with severe haemophilia A need CVADs (personal communication, H.M. Van den Berg).

Due to the high cost of factor concentrates and the fact that until now, prophylaxis had to be administered very frequently, prophylaxis remains very expensive – prohibitively expensive for most of the world. Lower dose/lower frequency prophylaxis regimens
have shown substantial decreases in bleeding frequency while using much less factor than in full-dose prophylaxis [30].

The short half-life of currently licensed factor concentrates creates a great need and a great opportunity for biologically engineered longer acting factor concentrates. These products might address some of the main limitations of current concentrates and lead to improved adherence to prophylaxis.

**Prophylaxis beyond 2014**

Several methodologies are currently being used to extend the half-life of factor. These technologies can be divided into two major categories: conjugation of clotting factors to polyethylene glycol (PEG), and fusion of clotting factors to albumin or the Fc component of immunoglobulin G (IgG) [31,32].

Pegylation of proteins is a technology that goes back about 20 years; Cimzia and Neupogen are two of the many pegylated products in clinical use [33]. Pegylation involves the attachment of PEG molecules to create a hydrophilic cloud around a protein, thereby increasing its effective size above the filtration size of the kidneys and leading to reduced renal clearance. In the case of full length FVIII, the plasma FIX level would not fall below 1% for at least 10–22 days. This is a stark contrast to currently available FIX concentrates, which need to be given at least twice/week to maintain a trough level of >1%.

The other main technology is Fc or albumin fusion technology. Both albumin and IgG have long natural half-lives of about 3 weeks. Their long half-lives are mediated through the neonatal Fc receptor (FcRn) within monocytes/macrophages and endothelial cells. All plasma proteins are internalized by these cell types and targeted to the lysosome for destruction back to their constituent amino acids. However, albumin, IgG, and proteins to which albumin or the Fc portion of IgG is molecularly fused are protected from degradation and subsequently recycled back into the circulation. The end result of this is an extension of the half-life of FVIII and FIX. Etanercept and romiplostin are examples of currently licensed long-acting Fc fusion proteins, while albiglutide and neugranin are albumin fusion proteins currently in development [31,32].

**Longer acting factor IX concentrates in development**

Three longer acting FIX’s are well advanced in clinical studies (see Table 1). These products have been shown to have higher recoveries (1.2–1.9 fold higher) and much longer half-lives (3–5.8 fold longer) in comparison to currently available rFIX or pdFIX. Using these products, investigators have shown that after a dose of 50 IU kg$^{-1}$, the plasma FIX level would not fall below 1% for at least 10–22 days. This is a stark contrast to currently available FIX concentrates, which need to be given at least twice/week to maintain a trough level of >1%.

**Longer acting factor VIII concentrates in development**

There are at least four longer acting FVIIIs currently in development (see Table 1). These have shown a half-life prolongation of only 1.4–1.7 fold compared

### Table 1. Current long-acting FIX and FVIII concentrates well into clinical studies.

<table>
<thead>
<tr>
<th>Product</th>
<th>Technology</th>
<th>Manufacturer</th>
<th>Cell line for manufacture</th>
<th>$T_{1/2}$ (hrs)</th>
<th>$T_{1/2}$ vs. native FVIII/FIX</th>
<th>Estimated time to 1% after dose of 50 U/kg (in humans)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Longer acting FIX concentrates</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N9-GP [43,44]</td>
<td>Site-specific glycopegylation with a 40 kDa PEG molecule</td>
<td>Novo Nordisk</td>
<td>CHO</td>
<td>96–110</td>
<td>&gt;5 fold</td>
<td>22 day</td>
</tr>
<tr>
<td>rFIXe [36,45]</td>
<td>Fusion protein with Fc fragment of IgG</td>
<td>Biogen Idec</td>
<td>HEK</td>
<td>57–83</td>
<td>3 fold</td>
<td>10.1 day</td>
</tr>
<tr>
<td>rIX-FP [46]</td>
<td>Fusion protein with albumin</td>
<td>CSL Behring</td>
<td>CHO</td>
<td>89–96</td>
<td>&gt;5 fold</td>
<td>2–3 week (5% FIX level at day 14)</td>
</tr>
<tr>
<td>Longer acting FVIII concentrates</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BAY-94-9027 [33]</td>
<td>Site-specific glycopegylation (60 KDa PEG) of a B domain-deleted FVIII</td>
<td>Bayer</td>
<td>BHK</td>
<td>19</td>
<td>1.4 fold</td>
<td>NA</td>
</tr>
<tr>
<td>BAX 855 [47]</td>
<td>Controlled pegylation (2-20 kDa branched chain PEG) of a full-length FVIII</td>
<td>Baxter</td>
<td>CHO</td>
<td>NA</td>
<td>1.5 fold</td>
<td>NA</td>
</tr>
<tr>
<td>N8-GP [48]</td>
<td>Single site-specific glycopegylation (40 kDa PEG) of a B domain-truncated (21 aa) FVIII</td>
<td>Novo Nordisk</td>
<td>CHO</td>
<td>19</td>
<td>1.6 fold</td>
<td>6.5 day</td>
</tr>
<tr>
<td>FVIII-Fc [37,49]</td>
<td>B domain-deleted FVIII fused to a monomeric Fc fragment of IgG</td>
<td>Biogen Idec</td>
<td>HEK</td>
<td>18.8–19</td>
<td>1.5–1.7 fold</td>
<td>4.9 day</td>
</tr>
</tbody>
</table>

CHO, Chinese hamster ovarian; BHK, baby hamster kidney; HEK, human embryonic kidney; NA, not available.
to currently licensed FVIII concentrates. This modest prolongation of half-life (compared with longer acting FIXs) is mainly related to the dependence of FVIII clearance on the clearance of VWF, which is not altered by using longer acting FVIII [3].

**Impact of longer acting factor concentrates on prophylaxis**

With the advent of longer acting factor concentrates, prophylaxis regimens will almost certainly change. This will involve changes in what trough levels are targeted and how frequently factor is administered. These products will cause investigators to consider the relative importance of trough vs. peak levels in the effectiveness of prophylaxis [14]. Changes in regimens may improve patients’ adherence to prophylaxis and patients’ quality of life. Definitions of the minimum infusion frequency to still be considered prophylaxis will obviously change, as will definitions for full, intermediate, and low-dose prophylaxis. Finally, these long-acting factor concentrates will undoubtedly have cost repercussions and, given that these products will be substantially different from each other, they will raise important questions regarding how decisions about choosing one longer acting concentrate over another, and whether these products are interchangeable, are made. The following sections will deal with each of these implications of longer acting factor concentrates.

**Impact on prophylaxis regimens, adherence to prophylaxis and quality of life**

**Decreased number of infusions**

With these newer concentrates, patients will have the option of lengthening the interval between infusions while still achieving a factor trough level of >1%. Patients with severe haemophilia B who currently may take two infusions/week (104 infusions/year) might be just as protected from bleeds with perhaps one infusion every 1–3 weeks (18–52 infusions/year) [36]. Patients with severe haemophilia A might be able to receive two infusions/week (102/year) or one infusion every 3–5 days and still maintain a trough level of >1% [37]. This compares to current regimens, where on full-dose prophylaxis patients with severe haemophilia A will receive 156–182 infusions annually (3–3.5 infusions/week). Decreasing the number of infusions should reduce the need for CVADs (and their consequent sequelae). A further benefit of decreasing the number of infusions is that when commencing patients on prophylaxis, fewer clinic visits will be required for those patients/families who are as yet unable to infuse factor at home. It will also reduce home care nurse visits where this is an option. All of this may translate into earlier start of prophylaxis, fewer missed doses, and overall better bleed protection. There may also be drawbacks to maximizing the interval between infusions, as it will result in patients having low factor levels for extended periods of time during which they may be physically active and at risk of bleeding.

**Higher troughs**

Until now, the relatively short half-lives of factor concentrates and their very high cost precluded patients maintaining trough levels during prophylaxis (even on full-dose prophylaxis) of much higher than 1%. Although such trough levels have been demonstrated to reduce the frequency of spontaneous bleeds, they certainly do not protect against traumatic bleeds where higher factor levels are required [38]. Longer acting FIXs currently under development should permit patients to consider having trough levels that are substantially higher than 1%. This may facilitate much more active lifestyles (permitting greater levels of sports and work participation) while still maintaining a low risk of bleeding. Of course, it is not known what trough level to target. Presumably the higher the trough level targeted, the less risk of bleeding and the more active the patient can be without the worry of bleeding but with the trade-off of higher cost and more infusions [39].

**Decreased infusions vs. higher troughs vs. combination of both**

With these products, patients/families may opt to minimize the number of infusions (lengthening the interval between infusions) while still maintaining the trough level of >1%, or they may opt for more frequent dosing to achieve trough levels that are substantially higher than 1%. Ultimately, some patients might choose one or another or a hybrid depending on their lifestyle: lengthening the interval between infusions as much as possible may be preferred in less active children/adults, very young patients (e.g. infants) just starting on prophylaxis, and those with poor venous access. More active patients, particularly those with good venous access, might choose to receive more frequent infusions to achieve higher trough levels. All of this leads to increased individualization of prophylaxis.

**Prophylaxis regimens**

Until now, with current concentrates, it has been recommended to infuse factor in the mornings [11]. This can be quite burdensome to families who are rushing to get their children to school and themselves to work. With longer acting factor concentrates (particularly
PEG molecules are cleared through the liver and the kidneys and excreted in the urine, while larger molecules are cleared according to their molecular weight. Smaller PEG molecules (<30 kDa) are cleared through the kidneys and excreted in the urine, while larger PEG molecules are cleared through the liver and excreted in the faeces. Recent ongoing animal studies using radio-labelled PEG show that even larger PEG molecules are excreted in the urine (personal communication, Mathew P, Bayer). Animal autopsy studies have identified PEG present in inclusions within the reticuloendothelial system, renal tubular epithelial cells and the choroid plexus of animals receiving extremely high doses of PEG, but the clinical implications of this remain unknown at the present time [33]. As there have not been any PEG conjugated products used on a weekly (or more frequent) basis over the entire life of a person, concerns remain as to whether there may be some long-term tissue/organ accumulation of PEG. However, it must be noted that the amount of PEG in current factor concentrates is approximately 1000-fold less than that used in animal studies [33]. Furthermore, no PEG-related toxicities have been reported among the medications currently in clinical use in other disease states [33]. No specific safety issues have been reported with albumin or Fc fusion proteins related to the albumin or Fc molecules.

For some of the longer acting FIX and FVIII concentrates, small changes in FIX and FVIII are required to introduce sites for pegylation or to allow for fusion to albumin or Fc. There is some concern that this might increase the immunogenicity of the factor. However, inhibitor development has not been reported to date in either ongoing or completed clinical trials involving previously treated patients (PTPs) with longer acting factors. Furthermore, some animal studies suggest that pegylation may shield epitopes and Fc may be immune-modulatory, thus potentially reducing overall immunogenicity [33,35,42].

**Increased use of prophylaxis**

Longer acting concentrates may result in patients currently treated on demand now opting to be on prophylaxis. In particular, patients with severe or moderate haemophilia B who are currently treated on demand may opt to receive one prophylactic infusion every 2–3 weeks (18–26 infusions/year). Others who are currently not on prophylaxis may choose to be on prophylaxis during certain time periods: when travelling or during particular times of the year when they might be more physically active: e.g. summer. Currently, patients not on prophylaxis (some severe and most moderate) when they travel incur the risk of bleeding and then need medical attention. Such patients with haemophilia B may, with these products, choose to receive a dose of a longer acting factor prior to travelling, which would protect them while they are away. This might greatly relieve patient/family anxiety regarding experiencing a bleed while travelling.

**Improved quality of life**

With longer acting factor concentrates allowing patients to infuse much less frequently, and with potentially higher trough levels allowing for greater participation in physical activity, the presumption is that patient/family quality of life will be improved. Of course this needs to be evaluated in well-designed prospective studies.

**Safety issues with longer acting factor concentrates**

So far no major safety concerns have arisen with pegylated factor concentrates. However, hypersensitivity reactions to PEG have been reported. Also, pre-existing anti-PEG antibodies have been identified in healthy blood donors and anti-PEG antibodies have been induced in a clinical trial of PEG-asparaginase [40]. It has been speculated that such anti-PEG antibodies may lead to rapid clearance of PEG conjugates [41]. So far this has not been observed with other pegylated compounds in clinical use or with pegylated factor concentrates in ongoing clinical trials [33].

PEG is cleared according to its molecular weight. Smaller PEG molecules (<30 kDa) are cleared through the kidneys and excreted in the urine, while larger PEG molecules are cleared through the liver and
concentrates are not likely to be less expensive. However, they may result in the price of currently licensed products being reduced to continue to be somewhat competitive with the newer, longer acting products. Perhaps this will then allow developing countries to begin adopting more prophylaxis.

Impact on choice of long-acting products for prophylaxis

One of the major questions that physicians will have to ponder is how will they choose a longer acting FVIII or FIX concentrate, once these products are licensed. Until now, when choosing a FVIII or FIX concentrate, the big question has generally been whether to choose a plasma-derived or a recombinant product. The main drivers of this decision have been cost, availability of product, the wish to avoid exposure to plasma-derived products and the (unproven) perception of differential rates of inhibitor development with different products. For the most part, currently available rFVIIIIs have been viewed as all being equally safe and effective and therefore virtually interchangeable. Consequently, patients have often switched from one product to another. Furthermore, until recently there had been no choice for rFIX concentrates as there had only been one available.

Longer acting factor concentrates currently in development are all recombinant but otherwise are substantially different from one other. They are different with respect to the actual FVIII (full length vs. B domain-deleted vs. B domain-truncated), with respect to the technology used to extend the half-life (pegylation using different size PEG molecules, or fusion technology using either Fc or albumin) and with respect to the cell lines in which they are manufactured (Chinese hamster ovarian, baby hamster ovarian, human embryonic kidney). How will the comparative pharmacokinetics of different factor concentrates impact on the choice of factor concentrate? Will the product with the longest half-life always be preferred or will the manufacturing technology and perceived safety concerns override the pharmacokinetics? Also, will families/healthcare providers feel comfortable starting previously untreated patients on all, or some, of the longer acting FVIII or FIX concentrates or will they hold off until a certain number of exposures to currently available factor concentrates have occurred? Will it still be acceptable to switch patients from one longer acting concentrate to another?

Conclusions

Much is likely to change regarding prophylaxis with the advent of these bioengineered longer acting factor concentrates. There will be a great need for well-designed, prospective, multi-centred studies that look closely at outcomes, quality of life and cost. Of course with any new product there must remain an ongoing scrutiny to look for any potential safety issues with these agents. Long-acting factor concentrates represent a major advance in the management of haemophilia. And yet these molecules are likely to be only stepping stones, given the future potential of manufactured products with even longer half-lives, of these products being partnered with therapies such as tissue factor pathway inhibitors (TFPI), and of subcutaneous or even oral delivery of such products. In addition to this, gene therapy is becoming a closer reality. As such, the next 10–20 years are likely to bring a plethora of activity in the area of prophylaxis in haemophilia and hopefully will further improve the lives of people with haemophilia.

Acknowledgements

I am grateful to the following people who reviewed this paper and provided some helpful feedback: Len Valentino and Bruce Ewenstein (Baxter); Prasad Mathew (Bayer); Glenn Pierce (Biogen); Debbie Bensen-Kennedy and Henry Mead (CSL Behring); and Karin Knobe and Stephanie Seremetis (Novo Nordisk).

Disclosures

M. Carcao has received honoraria/speaker fees and grant support from Bayer, Baxter, Biogen, CSL Behring, Novo Nordisk, Octapharma and Pfizer. He has also participated in industry sponsored research studies on long acting factor concentrates from Bayer, Biogen and Novo Nordisk.

References