Optimal trough levels in haemophilia B: Raising expectations

Haemophilia is a rare X-linked disorder characterized by a deficiency or dysfunction in circulating coagulation factor VIII or IX. Patients with severe haemophilia are at an increased risk of spontaneous bleeding predominantly into the joints, potentially leading to arthropathy and chronic disability. Haemophilia B is often assumed to be less phenotypically severe than haemophilia A. There has been extensive research and discussion on the value of trough levels in haemophilia A, and many physicians use trough levels as a guide to develop individualized treatment regimens. We read with interest the letter published in Haemophilia from Gill et al, which demonstrated that high trough levels were achievable in patients treated with rIX-FP (IDELVION®; CSL Behring), an extended half-life albumin fusion protein, on an extended dosing regimen.¹

This letter intends to build on this data and provoke thought around individualizing treatment, using trough levels as a guide to provide optimized treatment for patients with haemophilia B. It has previously been shown that increased time spent below 1% FIX activity is associated with a higher bleeding rate,² but a trough level capable of preventing all bleeds has not been determined for patients with haemophilia B. Target trough levels for patients with haemophilia A have been widely discussed; it is important to also consider these conversations for patients with haemophilia B.

Recent experience has shown that patients with haemophilia B treated with extended half-life (EHL) FIX products can still experience breakthrough bleeding, despite seemingly adequate trough levels. This phenomenon is also seen in patients with mild haemophilia A and those treated with gene therapy. These data suggest that current trough-guided dosing protocols are inadequate to achieve zero bleeding for all patients. An abstract presented at the 27th annual Congress of the International Society on Thrombosis and Haemostasis, 2019, suggested that extravascular levels of rIX-FP are lower than with other EHL FIX products and this may be a reason for unexpected bleeding.³ However, their analysis was subject to a number of limitations, including a low number of participating Hemophilia Treatment Centers (HTCs) and a lack of data on patients’ baseline data; and, as such, the context of these data is as yet undetermined. This narrative has also been discussed in a recent letter as a potential explanation for uncontrolled bleeding that has been reported in three patients who were switched from twice-weekly rFIX to rIX-FP administered every 14 days.⁴ Again, a number of issues with this report bring into question the validity of the hypotheses presented. One of the most concerning issues was that the switching protocol was not in line with the rIX-FP product label, which states that patients should be well controlled on a 7-day dosing regimen before switching to an extended dosing regimen. Additionally, their letter reports that all other patients currently treated with rIX-FP at that HTC (n = 22) are doing well on an extended dosing regimen.

Stafford et al identified that collagen IV binds extracellular FIX.⁵ In that study, FIX knockout mice carried the majority of FIX extracellularly and plasma FIX levels did not correlate with bleeding. Mice genetically engineered with a FIX with poor collagen binding had a higher bleeding rate despite high plasma FIX levels. These data suggest that tissue distribution of FIX affects bleeding outcomes. Suggestions that the volume of distribution for each EHL FIX may explain tissue distribution and bleeding still begs the question as to the mechanism that regulates the local concentration of active FIX at sites of bleeding. FIX levels in the plasma versus the extravascular space have never been rigorously studied in humans and, as such, a causal relationship is still to be determined. FIX is found in the extravascular space (whether it contributes to clinical efficacy or not) and cannot be measured by pharmacokinetic assessments; therefore, trough levels may not directly correlate with the amount of FIX present in the tissues. While pathophysiology is interesting, there is currently insufficient evidence to support the hypothesis that increased FIX in the extravascular space improves haemostatic efficacy in patients with haemophilia B, especially since activated FIX is required at the site of bleeding.

Despite these potential differences in extravascular distribution, all EHL FIX products have shown excellent efficacy in clinical trials.⁶⁻⁸ Differences in extravascular distribution observed across FIX products may also be due to variances in measurement parameters. In particular, inconsistency in pharmacokinetic (PK) models utilized across clinical trials makes indirect comparisons unreliable, and the introduction of multi-compartmental models and longer sampling times for the pharmacokinetics of EHL FIX have made the routine pharmacokinetic studies used in clinical trials unsatisfactory.⁹ Additionally, different aPTT reagents have been shown to have varied performance across different FIX molecules.⁹ Comparisons across studies must fully consider the comparability of the population and PK models utilized before drawing robust conclusions.

Circulating factor levels are used to determine dosing regimens, and higher circulating FIX levels are generally associated with improved clinical outcomes. Although espousing a minimum plasma FIX level that protects patients from all bleeding would be...
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TABLE 1 Reported trough levels of extended half-life FIX products during clinical trials

| Regimen  | Dose (IU/kg) | Mean trough levels at steady-state FIX:C (%) | Median ABR (IQR) | Median AsBR (IQR) |
|----------|--------------|---------------------------------------------|------------------|------------------|
| rIX-FP 1 | 7-d 33       | 35-50 21                                   | 0.00 (0.00, 1.87) | 0.00 (0.00, 0.00) |
|          | 14-d 16      | 50-75 13                                   | 1.08 (0.00, 2.70) | 0.00 (0.00, 1.00) |
| rFIXFc 7 | 7-d 50       | 20-100 NR                                  | 2.28 (0.44, 3.76) | 0.82 (0.00, 2.65) |
|          | 13.7-d6 30   | 100 NR                                     | 2.25 (0.87, 4.47) | 0.68 (0.00, 2.58) |
| N9-GP 6  | 7-d 29       | 40 27                                       | 1.04 (0.00, 4.01) | 0.00 (0.00, 0.99) |

Abbreviations: ABR, annualized bleeding rate; AsBR, annualized spontaneous bleeding rate; IQR, interquartile range; NR, not reported.

Individualized dosing based on median dosing interval.

satisfying, it is likely to vary from patient to patient based on joint status, age, intercellular transport, interstitial binding and other factors. Recent gene therapy data would also suggest that despite constant levels of FIX, ranging from 3.0% to 12.7%, enabling the cessation of prophylaxis, bleeding is reduced but not eliminated.10 The prevention of permanent disability should be the primary aim of an optimal treatment plan; however, the time taken to develop these issues is outside the scope of most clinical studies. Annualized bleeding rates are often used as a surrogate marker for joint status, and the development of improved FIX products and monitoring practices has made it evident that in addition to trough levels, other PK outcomes, including peak levels, half-life and area under the curve, may also provide important predictors regarding a patients’ long-term joint health.

Different FIX levels will be ‘optimal’ in different clinical situations, such as for perioperative management or during periods of high physical activity. In addition, the aim of prophylaxis may not be to achieve higher trough levels in all patients; patients with existing joint disease or more sedentary lifestyles may instead prefer treatment tailored to improve mobility or less frequent dosing. If increased troughs are the primary treatment aim, it is of course essential to ensure that increased trough levels are correlated with improved clinical outcomes, as both over- and under-prescribing FIX treatment can be detrimental to clinical and socio-economic outcomes. Currently, clinical guidelines suggest to aim for a baseline trough of >1% FIX activity when treating patients with haemophilia B. However, this is generally insufficient to prevent all bleeding, especially during periods of increased bleeding risk.

The evidence regarding FIX trough levels in clinical trials is limited; Table 1 shows available data in adult and adolescent patients with haemophilia B treated with EHL FIX products. Trough levels were not routinely measured in the rFIXFc (Alprolix®; Bioverativ) trials; however, dosing was adjusted to maintain a target trough level of ≥1%-3%.7 The rFIXFc clinical trial had the lowest target trough levels of the EHL FIX products evaluated, and the median ABR point estimates suggests the highest bleeding rates8; Novo Nordisk), and median (IQR) annualized spontaneous bleeding rate (AsBR) was 0.0 (0.00, 0.00) and 0.0 (0.00, 0.99), respectively.1,6 Additionally, patients treated with 14-day rIX-FP prophylaxis reported a median (IQR) AsBR of 0.0 (0.00, 1.00) with steady-state trough levels of 13%,1 which is significantly above the recommended target of 1%. Although these results cannot be directly compared due to the differences in study populations and they do not provide us with a defined optimal trough level, the data may suggest that lower bleeding rates are correlated with increasing trough factor levels.

It appears that a ‘one size fits all’ approach to optimal trough factor levels is not appropriate. While it is evident that a number of patients can be well managed on lower trough levels, it is also clear that, while reduced, bleeding still occurs in patients with high trough levels. This confirms that dedicated research needs to be conducted into the relationship between trough factor levels and treatment efficacy in patients with haemophilia B.

While there are a number of articles citing a beneficial link between extravascular FIX and hemostasis, the role of extravascular FIX is unclear as yet and should be further explored.3,5 What is evident is that all EHL FIX concentrates can provide flexible dosing with high trough levels and good clinical efficacy, which may result in improved clinical outcomes for patients with haemophilia B. With the evidence that is currently available, it would be premature to define an optimal plasma FIX level to prevent all bleeds in all patients with haemophilia B. Instead, clinical efficacy should remain the most important outcome measure of treatment success and trough factor levels should be considered in an individualized treatment plan.

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