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High adherence to prophylaxis regimens in haemophilia B patients receiving rIX-FP: Evidence from clinical trials and real-world practice

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Abstract

Introduction: Adherence to prophylaxis regimens is essential for bleed prevention in haemophilia but remains a challenge due to the need for frequent infusions.

Aim: To evaluate patient adherence to prophylaxis regimens with a long-acting recombinant factor IX (rIX-FP; IDELVION®) in clinical studies and real-world practice.

Methods: In two phase 3 clinical studies, patients with haemophilia B (FIX ≤2%) recorded their dose, dosing frequency and rIX-FP consumption in an e-diary. Adherence to prescribed prophylaxis regimens was assessed in all patients and to prescribed dose in patients ≥12 years only. Additionally, adherence to rIX-FP prophylaxis regimens in real-world practice was captured.

Results: In clinical studies, 94.9% (n = 56/59) of patients ≥12 years and 100% (n = 27) of paediatric patients received ≥80% of the expected number of infusions for their assigned prophylaxis schedule. Overall, mean adherence rate was 95.5% across all prophylaxis regimens in patients ≥12 years and 97.9% with a 7-day regimen in paediatric patients. In patients ≥12 years, 85.7% (n = 54/63) were dose adherent, defined as receiving within 10% of their prescribed dose ≥80% of the time. In real-world practice, adherence was observed in 100% (n = 14 and n = 15, respectively) of patients in two haemophilia treatment centres and 57.1% (n = 4/7) of patients in a third centre; non-adherence (n = 3/7) was linked to insurance-related and parental issues.

Conclusion: In clinical studies, patients with haemophilia B had high adherence rates to rIX-FP prophylaxis regimens with a variety of dosing intervals, enabling them to achieve very low bleeding rates. High adherence may also be achievable in real-world practice.

KEYWORDS

adherence, albutrepenonacog alfa, factor IX, haemophilia B, rIX-FP, treatment

1 | INTRODUCTION

Haemophilia is typically treated with coagulation factor replacement therapy either prophylactically or on-demand. For severe disease, prophylaxis is the standard treatment regimen as it has been shown to improve health outcomes compared with episodic treatment, including reductions in the frequency of total and joint bleeding events, prevention of life-threatening bleeds and preservation of joint function.[1,2] These improved outcomes can only be achieved and maintained with adherence to prescribed prophylaxis regimens. However, rigorous prophylaxis regimens, and the need for frequent intravenous infusions, are a significant burden for patients and can result in reduced patient adherence. Furthermore, the leading reasons reported by patients for non-adherence to their prescribed regimen included lack of time for treatment and convenience.[3] Infusion schedules should, therefore, be simple to implement and acceptable to the patient, taking into consideration their lifestyle and activities.[4]

The availability of extended half-life recombinant factor IX (rFIX) concentrates is beginning to change the treatment paradigm for prophylaxis in haemophilia B.[5] Extended half-life products are improving and facilitating prophylactic therapy in patients with haemophilia B by permitting the maintenance of higher trough levels (FIX >5% or >10%) whilst reducing the frequency of infusions with injections once weekly or once every 2 weeks.[6] Therefore, these products have the potential to decrease the burden of prophylaxis, which may lead to improved adherence and ultimately improved health outcomes.[4]

rIX-FP (IDELVION®) is a fusion protein genetically linking recombinant human coagulation factor IX (FIX) with recombinant human albumin.[7,8] It was designed to have an improved pharmacokinetic profile compared with standard FIX; thus, allowing less frequent dosing.[9] In the PROLONG-9FP clinical trial program, rIX-FP prophylaxis achieved median annualized spontaneous bleed rates of 0.00 with 7-, 10- or 14-day dosing intervals in adults (≥12 years) and 7-day dosing interval in children (<12 years).[7,8]

Here, we evaluated the adherence to different rIX-FP regimens in two phase 3 clinical trials in patients with haemophilia B. In addition, real-world practice data on patient-reported adherence to prescribed prophylaxis schedules collected in patients receiving rIX-FP prophylaxis at three expert haemophilia treatment centres are presented.

2 | MATERIALS AND METHODS

2.1 | Clinical studies

2.1.1 | Study population

The detailed study designs of the adolescent/adult (NCT0101496274) and paediatric (NCT01662531) rIX-FP phase 3 studies in previously treated patients with haemophilia B (FIX ≤2%) have been described previously.[7,8] Briefly, patients aged 12-65 years received 7-day rIX-FP prophylaxis (35-50 IU/kg) for 6 months then either continued with 7-day prophylaxis or extended their dosing interval to 10 or 14 days at a dose of 75 IU/kg, if they met switching criteria (prophylaxis arm; n = 40). Alternatively, patients started with on-demand treatment with rIX-FP for 6 months followed by 35-50 IU/kg rIX-FP every 7 days (on-demand arm; n = 23).[7] Paediatric patients (<12 years; n = 27) received 35-50 IU/kg rIX-FP prophylaxis every 7 days for a minimum of 12 months.[8] During both studies, dosing could be adjusted based on bleeding phenotype, physical activity level and clinical symptoms.[7,8]

2.1.2 | Measuring treatment adherence

In both clinical studies, patients used an e-diary to record dose, dosing frequency and rIX-FP consumption for both prophylaxis and on-demand treatment. In the case of paediatric patients, the e-diary may have been completed by their caregiver. Patients returned their used vials at every study visit and unused vials at, or prior to, the end of the study. Treatment adherence was monitored by counting the number of used and unused vials and reconciling with that reported in the e-diary.

Prophylaxis adherence was determined in terms of schedule in all patients and defined as receiving ≥80% of the expected number of injections for the assigned prophylaxis schedule:

$$\text{Prophylaxis adherence} = ([\text{No. of prophylaxis infusions during the treatment period}]/[\text{Expected no. of prophylaxis infusions during the treatment period based on treatment regimen}]) \times 100$$

Dose adherence was determined in terms of prescribed dose in patients ≥12 years only and defined as receiving within 10% of the prescribed dose ≥80% of the time:

$$\text{Dose adherence} = ([\text{No. of doses within 10\% of the prescribed dose}]/[\text{No. of doses}]) \times 100$$

2.2 | Real-world practice

Data on adherence to prescribed prophylaxis schedules were collected in patients receiving rIX-FP prophylaxis at three expert haemophilia treatment centres: Rush Hemophilia and Thrombophilia Center, Rush University Medical Center, Chicago, IL, USA; Angelo Bianchi Bonomi Hemophilia and Thrombosis Center, Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico, Milan, Italy; and Hemophilia Center University Clinic Bonn, Bonn, Germany. None of the patients included were receiving, or had previously received, rIX-FP as part of a clinical trial.

2.2.1 | Measuring patient-reported adherence

At the Rush Hemophilia and Thrombophilia Center, patient-reported adherence was measured by conducting a review with the patient. In addition, the patient infusion log was assessed and both written prescriptions (times and dates) and prescriptions filled from pharmacy records were evaluated. In the other two centres (Milan and Bonn),

patient-reported adherence was measured by matching the patient infusion log with the prescribed regimen. At variance with the clinical trials, there was no direct control of vial consumption at any of the centres. Although the Rush Hemophilia and Thrombophilia Center controlled for vial distribution, filled prescriptions from pharmacy records were reconciled with the patient infusion log.

3 | RESULTS

3.1 | Clinical studies

3.1.1 | Patients ≥12 years, prophylaxis arm

The proportion of patients who were adherent with their prescribed dose, those who received within 10% of the prescribed dose ≥80% of the time, was highest with the 7-day regimen (95.0%), and was 85.7% and 81.0% with the 10- and 14-day regimens, respectively. On the 14-day regimen, the mean (standard deviation [SD]) monthly rIX-FP prophylaxis dose was 157.4 (16.3) IU/kg, ranging from 111.8 to 179.1 IU/kg, indicating that the majority of doses administered were consistent with the assigned dose of 75 IU/kg. The monthly rIX-FP prophylaxis dose on the 7- and 10-day regimens was 202.7 (SD 47.9; range 139.9-321.5) IU/kg and 201.5 (SD 42.5; range 131.6-238.9) IU/kg, respectively.

Of the patients in the prophylaxis arm, 94.9% (56/59) met the definition of being adherent with their prophylaxis regimen, in that they received ≥80% of the expected number of infusions for their assigned prophylaxis schedule. The proportion of adherent patients was high with all regimens but particularly where infusions could be scheduled on the same day of the week; 97.5% (39/40) and 100% (n = 21) of patients were adherent with 7- and 14-day regimens, respectively. A relatively small number of patients (n = 7) received a 10-day regimen during the study with 85.7% of patients being adherent; however, this reflects the fact that only one of the seven patients did not meet the definition of adherence. Mean dose and prophylaxis adherence rates for each regimen are shown in Table 1.

3.1.2 | Patients ≥12 years, on-demand arm

During the first 6 months of the study, 23 patients received rIX-FP on-demand. During this period, the proportion of patients that were considered adherent with their prescribed doses was low (52.2%). After switching to 7-day prophylaxis (n = 19), the proportion of these patients who were dose adherent substantially increased to 84.2%. Of these patients, a high proportion (89.5%) was also adherent with their prophylaxis schedule once they had switched.

3.1.3 | Paediatric patients

All 27 (100%) paediatric patients were adherent with a 7-day rIX-FP regimen, with a mean (SD) adherence rate of 97.9% (3.78) and similar adherence rates between age groups; mean (SD) 97.3% (4.80) in patients 1-5 years and 98.3% (2.82) in those aged 6-11 years. High levels of adherence to a 7-day regimen resulted in low bleeding rates in paediatric patients, as previously reported.[8]

3.2 | Real-world data

A total of 36 patients (≥12 years, n = 26; <12 years, n = 10) from three centres were analysed, including seven patients treated at the Rush Hemophilia and Thrombophilia Center, 14 patients treated at the Angelo Bianchi Bonomi Hemophilia and Thrombosis Center and 15 patients treated at the Hemophilia Center University Clinic Bonn. The proportion of patients adherent to their prescribed rIX-FP regimens at the three centres were 57.1% (n = 4/7) at the Rush Hemophilia and Thrombophilia Center and 100% (n = 14 and n = 15) at the other two centres, respectively. Due to the variation in data collection between the centres, which in contrast to a clinical study is non-standardized, only a description of the data is presented; refer to Table 2 for more patient and treatment details.

TABLE 1 Adherence to rIX-FP treatment regimens in patients ≥12 y in the PROLONG 9-FP clinical trial program

	Prophylaxis arm			On-demand arm		
	7-d regimen (n = 40)	10-d regimen (n = 7)	14-d regimen (n = 21)	On-demand regimen (n = 23)	Prophylaxis regimen (n = 19)	Total[a] (n = 63)
Prophylaxis adherence (%)						
Mean (SD)	94.7 (5.16)	90.7 (12.08)	97.2 (3.21)	N/A	95.5 (7.49)	95.5 (5.44)
Range	75.0-100	66.7-100	91.2-102.4	N/A	75.8-100	75.0-100
Dose adherence (%)						
Mean (SD)	96.4 (7.60)	90.1 (11.23)	89.7 (16.14)	74.8 (27.69)	89.9 (21.73)	91.1 (13.52)[b]
Range	66.7-100	68.8-100	31.4-100	12.5-100	13.5-100	36.5-100

Abbreviations: N/A, not applicable; SD, standard deviation.

[a]n = 59 subjects for prophylaxis adherence.

[b]Includes patients treated on-demand or with prophylaxis.

TABLE 2 Adherence to prescribed rIX-FP regimens in patients with haemophilia B treated at three haemophilia treatment centres

Centre	Rush Hemophilia and Thrombophilia Center (N = 7)	Angelo Bianchi Bonomi Hemophilia and Thrombosis Center (N = 14)	Hemophilia Center University Clinic Bonn (N = 15)
Number of patients, n			
≥12 y	4	11	11
<12 y	3	3	4
Age range, y	6-44	5-76	1-64
Dosing frequency	7 d: 40 IU/kg (n = 5) or 50 IU/kg (n = 2)	7 d: 28-45 IU/kg (n = 8) 10 d: 35-41 IU/kg (n = 2) 14 d: 50-58 IU/kg (n = 4)	7 d: 24-50 IU/kg (n = 15)
Overall treatment duration range, mo	10-24	9-22	4-31
Adherent patients, n (%)	4 (57.1)	14 (100)	15 (100)
Reasons for non-adherence	• Insurance challenges (n = 2) • Parental (n = 1)	N/A	N/A
Regimens in non-adherent patients	• On-demand through ED (n = 1)[a]	N/A	N/A

	Adherent patients (n = 4)	Non-adherent patients (n = 3)	Adherent patients (n = 14)	Adherent patients (n = 15)
Mean (SD) FIX trough level	8.4 (5.3)	7.4 (5.7)	14.2 (5.3)	10.6 (8.4)[b]
Median (range) ABR	0.50 (0.0, 1.0)	0.00 (0.0, 3.0)	0.00 (0.0, 1.5)	0.66 (0.0, 2.5)[c]
Patients experiencing bleeds, n	2	2	6	8
Type of bleeds (patients, n)[d]	Minor bleeds • Tooth loss (n = 1) • Joint bleed (n = 1)	Major bleed • Iliopsoas (n = 1)[a] Target joint bleed (n = 1) Joint bleed (n = 1)	Minor bleeds • Traumatic joint bleed (n = 3) • Spontaneous joint bleed (n = 2) Major bleed • Spontaneous joint bleed with synovitis (n = 1)	Traumatic bleeds • 5 muscle bleeds (n = 3) • 3 joint bleeds (n = 3) • 1 eye bleed (operation) (n = 1) Spontaneous joint bleed (n = 3) Joint bleed (n = 1) Data missing (n = 2)

Note: Major bleeding episodes were defined as a bleeding episode for which a patient required treatment at the haemophilia centre; bleeding episodes requiring no more than 1-2 doses were defined as minor bleeding episodes.

Abbreviations: ABR, annualized bleeding rate; ED, emergency department; FIX, factor IX.

[a]Patient discontinued rIX-FP prophylaxis due to loss of insurance, currently treated on-demand.

[b]Data missing for four patients.

[c]Data missing for two patients.

[d]Some patients experienced more than one bleed.

The reasons for non-adherence at the Rush Hemophilia and Thrombophilia Center were loss of insurance and insurance issues (n = 2), and parental challenges (n = 1). Insurance issues included a complete lack of insurance and insurance with a company that did not cover the factor concentrate. Parental challenges were related to lack of time and communication to motivate the child to adhere to their treatment regimen. In addition, only one parent was able to assist with the injection. The patient who was non-adherent due to loss of insurance has switched to an on-demand regimen.

Across the three centres, the overall treatment duration with rIX-FP ranged from 4 to 31 months. During this time, bleed rates or number of bleeds whilst receiving rIX-FP were low (Table 2).

4 | DISCUSSION

Prophylaxis adherence is an important consideration for physicians in their decision-making; the choice of product and infusion schedule should be acceptable to the patient, and be simple and easy to implement. Here, we show that rIX-FP prophylaxis resulted in high rates of adherence with all regimens in clinical studies, with 95% of patients ≥12 years and 100% of paediatric patients complying with their assigned infusion schedule. Adherence rates were slightly lower for the 10-day regimen compared with the 7- and 14-day regimens, suggesting adherence to treatment may be easier for patients to implement if doses are taken on the same day of each

week, rather than every 10 days; however, the numbers assessed here were too small to fully address this question. Furthermore, a slightly higher level of adherence to prophylaxis was also observed with a 7-day regimen in patients ≥12 years who were treated with prophylaxis throughout the study and prior to study entry, than in those who switched from on-demand treatment to a 7-day regimen during the study. This may reflect a period of adjustment to a more burdensome, albeit more effective, schedule. Thus, it may be important to work closely with the patients and their family at the time of switch from on-demand to prophylaxis to improve adherence. In addition, patients on a weekly prophylaxis regimen are those who require greater protection from bleeds or have had more breakthrough bleeds on a previous regimen; therefore, they may be more motivated towards adherence in terms of injection frequency and number of doses. Similar to the adherence rates observed for the treatment regimens, adherence to the prescribed dose was also high. These high rates of adherence are consistent with the low bleeding rates observed in these clinical studies.[7,8] However, by the very nature of a clinical study, with regular visits and monitoring of patients, adherence rates would be anticipated to be high. In addition, patients deemed unable to adhere to their treatment schedule may not be thought suitable for inclusion in a clinical study.

Therefore, data for patients being treated with rIX-FP in routine clinical practice were sought to examine patient's adherence to rIX-FP prophylaxis schedules assigned by their treating physician. Of note, none of the patients included were receiving, or had previously received, rIX-FP as part of a clinical trial. These data suggest that high patient-reported adherence is possible in real-world clinical practice, with 100% of patients achieving adherence at two centres. In the centre with a lower adherence, insurance challenges, including loss of insurance, was the main reason for non-adherence. Thus, healthcare system-related factors such as access to insurance, which have previously been reported as barriers to adherence,[4] may account for the difference in adherence between the three centres described here. However, patient numbers within each centre are small, and direct comparisons are not possible due to differences in data collection. In contrast to the clinical trials, there was no verification of the distribution and consumption of product in the majority of cases. Ideally, patient adherence would be assessed in haemophilia treatment centres on a regular basis to identify any barriers that prevent patients from receiving optimal therapy. Further studies are required to confirm the results.

Clinical studies of rFIX therapies have clearly demonstrated the efficacy of prophylaxis; depending on the product and dosing regimen used, reductions in annualized bleeding rates ranging from 83% to 91% compared with on-demand treatment have been reported.[10] Furthermore, evidence suggests that starting prophylaxis prior to the onset of joint bleeding is most effective in preventing arthropathy.[11] In order to achieve these outcomes, adherence to a prophylaxis schedule is essential. A number of studies have assessed physician- and patient-reported adherence with varying definitions; however, excellent adherence is commonly but arbitrarily defined as administering at least 75%-80% of doses/medication.[4,12] Reported levels of adherence to prophylaxis regimens in severe haemophilia are inconsistent and range between 30% and 87%.[3,4,13,14] Furthermore, in a study of patients with haemophilia A, adherence rates were shown to be highest in young children, particularly in those infused by a family member compared with those who self-infused.[13]

Despite the known benefits of prophylaxis, data show it can be a demanding medical regimen and adherence is imperfect.[15] The majority of patients who fail to adhere to their prophylaxis schedule report time commitment and inconvenience as the most significant challenges to adherence. An Internet survey of patients who are candidates for prophylaxis and their caregivers indicated that a product providing reduced frequency of administration had a larger impact on treatment choice than one that provided small changes in annual bleeding rate.[16] Therefore, as shown in this study, extended half-life products have the potential to improve adherence and patient acceptance of prophylaxis by reducing the infusion schedule burden. In addition, the reduction in infusion frequency may alleviate the difficulties with venous access, which is often challenging to achieve, particularly in young children; thus, reducing the need for central venous catheters or allowing their use to be discontinued at a younger age.[4] Preliminary data for patients from a Canadian Registry switching from a standard to an extended half-life product reported improved quality of life (in 70% of patients) and improved adherence (in 16% of patients) as reasons for switching.[17] Furthermore, 8% of patients switched with the goal of decreasing the frequency of bleeds occurring with standard-acting products.

5 | CONCLUSION

In patients with haemophilia, adherence to a prophylaxis schedule is essential for bleed prevention and improvement of outcomes in the long term. rIX-FP can extend dosing intervals and reduce the treatment burden in patients with haemophilia B. Data show that rIX-FP prophylaxis dosing regimens of 7-, 10- or 14-day intervals result in high rates of adherence and very low bleeding rates in both adult and paediatric patient populations. Although regimens based on weekly cycles tend towards better adherence, extended half-life FIX products are able to achieve higher trough levels (FIX >5% or >10%) with longer dosing intervals, which may increase the uptake of, and adherence to, prophylaxis regimens, ultimately improving health outcomes in patients with haemophilia. Initial data from haemophilia treatment centres confirm high adherence to rIX-FP prophylaxis regimens in real-world practice.

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