

Tailored therapy with turoctocog alfa pegol according to patient's lifestyle and hemorrhagic phenotype: from clinical trial to real-life

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ABSTRACT

Although the use of prophylaxis regimens with prolonged half-life factors is now widespread in the world of hemophilia A, there is a lack of real-life evidence on the impact of these products on joint health, adherence, and quality of life of patients. Turoctocog alfa pegol is a glycoPEGylated recombinant factor VIII (FVIII) with an extended half-life (EHL), developed for prophylaxis, treatment of bleeds, and perioperative management in patients with hemophilia A. We report here on three cases of three patients affected by severe hemophilia A, with variable bleeding phenotype and lifestyle, to describe our clinical practice on prophylaxis with turoctocog alfa pegol. As confirmed in our cases, FVIII trough levels remained coherent with those experienced in the registration trial after the switch to the commercial EHL drug. Moreover, the cases highlight how the current clinical management of hemophilia can personalize treatment in several specific conditions.

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Introduction

Thanks to the evolution of hemophilia treatments, recombinant factor VIII (rFVIII) with an extended half-life (EHL) is available nowadays. Thanks to modified pharmacokinetics (PK) and innovative tested therapeutic dosages and schemes, they allow the association of a reduced number of intravenous infusions with greater patient protection from bleeding events.

Despite the widespread use of prophylaxis regimens with EHL life factors, there is a lack of real-life evidence on the impact of these products on joint health, adherence, and quality of life of patients.

Turoctocog alfa pegol (N8-GP; Novo Nordisk A/S, Bagsvaerd, Denmark) is a glycoPEGylated rFVIII with an EHL. This drug requires less frequent dosing and has a half-life of up to 1.6-fold longer than standard FVIII products.¹⁻³

Turoctocog alfa pegol was approved by the United States Food and Drug Administration (adults/adolescents and children) and the European Medicines Agency (adults/adolescents) for prophylaxis, treatment of bleeds, and perioperative management in patients with hemophilia.^{4,5} Safety and efficacy in the prophylaxis and treatment of bleeds in adults/adolescents and children with severe hemophilia A have been demonstrated in the pivotal phase III Pathfinder 2 and 5 trials.^{1,6}

We report here three cases of three patients affected by severe hemophilia A, with variable bleeding phenotype and lifestyle, to describe our clinical practice on prophylaxis with turoctocog alfa pegol, in the Department of Hematology of Vicenza Hospital.

Case reports

First therapeutic scheme: every four days

The first subject is a patient with severe hemophilia A (baseline FVIII levels <1%), no history of inhibitor, severely disabling

hemophilic arthropathy, needing multi-district prosthetic surgery, with concomitant hepatitis C virus (HCV) infection, which has been eradicated.

The patient was treated with “on-demand” plasma FVIII concentrates from August 1993 until July 2012 (number of plasma FVIII exposures >150).

In July 2012, when he was 58 years old, he was enrolled in the Pathfinder 2 study (NN7088-3859), initially with the “on-demand” regimen at a dose of 50 U/kg, then from January 2013 with a prophylaxis regimen at a dose of 50 U/kg every four days and from June 2015 at a dose of 75 U/kg every seven days, according to the study protocol. FVIII trough levels were 1% with the one-stage method and 2% with the chromogenic method (weekly regimen).

In September 2020, the patient switched to the commercial drug, at a dose of 3000 U every four days (about 45 U/kg), with FVIII trough levels of 4% with the one-stage method and 5% with the chromogenic method. The patient reported good compliance and good control of chronic joint pain.

In March 2021, the patient’s good compliance, the absence of bleeding complications reported over the months and the patient’s almost sedentary lifestyle led to the decision to switch to a weekly treatment regimen.

FVIII activity results were assessed using the Web-Accessible Population Pharmacokinetics-Service-Hemophilia (WAPPS-Hemo).⁸

Two time points at 15 minutes and 72 hours post-infusion were used for the WAPPS-Hemo assessments.

The FVIII activity measurements for the PK assessments were performed using a chromogenic assay.

Table 1 shows the estimated FVIII plasma concentration (U/mL).

Second therapeutic scheme: weekly

The second subject is a patient with severe hemophilia A (baseline FVIII levels <1%), without a history of inhibitor, with eradicated HCV infection and ankle and right knee arthropathy.

This patient was initially on on-demand therapy with rFVIII; from 2009 he was on prophylaxis with rFVIII at the dose of 2000 U, twice a week.

He was enrolled in the Pathfinder 2 study (NN7088-3859) in August 2012, initially at the regimen of 50 U/kg every four days, then at about 70 U/kg every seven days, with the maintenance of FVIII through levels at 1% with the one-stage method and 2% with the chromogenic method.

No bleeding events occurred during the experimental study. Chronic joint pain in the ankle and right knee significantly improved.

Since July 2020, the patient has been in treatment with the commercial drug at the same therapeutic regimen (75 U/kg) with FVIII trough levels consistent with the product PK (FVIII trough levels of 2% with one stage method; 1% with the chromogenic method). No bleeding events were reported. The drug led to good control of chronic joint pain.

FVIII PK analysis was assessed using WAPPS-Hemo.⁸ A time point at 32 minutes post-infusion was used for the WAPPS-Hemo assessments. The FVIII activity measurements for the PK assessments were performed using a two-stage coagulation test (chromogenic method).

Table 2 shows the estimated FVIII plasma concentration (U/mL).

Third therapeutic scheme: biweekly

The third subject is a patient with severe hemophilia A, without a history of inhibitor, in prophylaxis since the age of 3 years with rFVIII twice a week. The patient had concomitant hemophilic arthropathy affecting the ankle and left knee.

He was enrolled in the Pathfinder 5 study (NN7088-3885) in February 2013 with a biweekly scheme. FVIII levels after 96 hours were 4% with the one-stage method and 6% with the chromogenic method.

During the study, the patient reported some hemorrhagic episodes, mainly of post-traumatic nature.

In July 2020, the patient was switched to the commercial drug, at the same therapeutic scheme and with substantially overlapping PK data (FVIII of 6% with the one-stage method, 5% with the chromogenic method after 96 hours). No bleeding events were reported.

FVIII PK analysis was assessed using WAPPS-Hemo.⁸ A time point at 32 minutes post-infusion was used for the WAPPS-Hemo assessments.

The FVIII activity measurements for the PK assessments were performed using a two-stage coagulation test (chromogenic method).

Table 1. Estimated factor VIII plasma concentration (U/mL), assessed by the Web-Accessible Population Pharmacokinetics-Service-Hemophilia. First therapeutic scheme.

Time, days	Conservative	Balanced	Optimistic
1	0.446	0.514	0.592
2	0.224	0.264	0.312
3	0.111	0.137	0.170
4	0.055	0.072	0.095
5	0.029	0.039	0.055
6	0.016	0.022	0.032
7	0.010	0.014	0.020
8	0.007	0.010	0.013

Table 2. Estimated factor VIII plasma concentration (U/mL), assessed by the Web-Accessible Population Pharmacokinetics-Service-Hemophilia. Second therapeutic scheme.

Time, days	Conservative	Balanced	Optimistic
1	0.837	0.3961	1.102
2	0.392	0.465	0.551
3	0.180	0.226	0.284
4	0.083	0.111	0.150
5	0.040	0.056	0.080
6	0.020	0.030	0.044
7	0.012	0.017	0.025
8	0.008	0.011	0.016
9	0.006	0.008	0.011

Table 3 shows the estimated FVIII plasma concentration (U/mL).

Considering the patient's lifestyle with the need to maintain higher trough levels, a bi-weekly regimen can be continued.

Discussion

The use of turoctocog alfa pegol in prophylaxis was associated with a particularly low number of bleeds in the Pathfinder study program, allowing to maintain in all patients a trough level of at least 3% with a therapy regimen of 50 U/kg every four days and allowing in some selected patients to reach a regimen of administration once a week with 75 U/Kg.⁷

In the described patients, FVIII trough levels remained consensual to their experience in the registration trial: since this is the center with the largest number of cases enrolled, observing the maintenance of results in real life is fundamental.

Moreover, the current cases highlight how the current clinical management of hemophilia can personalize treatment in several specific conditions: the treatment has been tailored according to the patient's lifestyle and hemorrhagic phenotype.

The first subject is a 66-year-old patient in tertiary prophylaxis with severe multi-district arthropathy already with multiple joint prostheses, low bleeding tendency, sedentary lifestyle and control of chronic joint pain from the beginning of prophylaxis with N8-GP. This drug led to a good management of orthopedic surgery. The same characteristics have been maintained with the commercial drug; therefore, after starting the dosage at about 50 U/kg, the patient was switched to weekly administration.

The second subject is a 48-year-old patient with severe hemophilia in secondary prophylaxis, with a low bleeding tendency and a sedentary lifestyle. The same characteristics of good adherence to treatment and good quality of life with weekly infusions were maintained even with commercial products, together with the same PK profile compared to the experimental product (slight discrepancies depending on the laboratory method – one stage versus chromogenic – however, possible in the case of low values). Considering the patient's characteristics, lifestyle and PK, he will go on with the established regimen.

The third subject is a 20-year-old patient in secondary pro-

phylaxis, with a very active, sporting lifestyle (horseback riding, athletics) and with a tendency to bleed, including post-traumatic ones.

Good adherence to treatment and good quality of life were reported, together with excellent coverage of the current therapeutic regimen, both within the experimental protocol and with the commercial drug. Considering the patient's lifestyle with the need to maintain higher trough levels, a bi-weekly regimen will be continued.

Before the switch to N8-GP, the bleeding tendency of the first and second patients was only modest, also in line with the sedentary lifestyle of both. However, especially in the first patient, due to advanced arthropathy with exacerbations of joint pain, "on-demand" infusions were frequent. The third patient, however, presented a high bleeding tendency, especially post-traumatic, in line with the very active lifestyle and sometimes high-impact sport. The switch to N8-GP allowed a clinical improvement in all three patients, reducing the number of additional infusions and the overall consumption of concentrates, resulting in an improvement in costs.

Conclusions

As confirmed in our cases, after the switch to commercial drugs, FVIII levels remained consensual to the ones experienced in the registration trial.

The cases highlight how the current clinical management of hemophilia may allow to personalize the treatment according to specific conditions, such as lifestyle and hemorrhagic phenotype, in order to improve adherence to treatment and its effectiveness. Good adherence to treatment and good quality of life were reported, together with excellent protection from bleeding.

These cases can be added to the limited body of evidence currently available on turoctocog alfa pegol in real life. Further investigation is required to study the impact of this product in real life.

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Table 3. Estimated factor VIII plasma concentration (U/mL), assessed by the Web-Accessible Population Pharmacokinetics-Service-Hemophilia. Third therapeutic scheme.

Time, days	Conservative	Balanced	Optimistic
1	0.693	0.794	0.911
2	0.349	0.413	0.489
3	0.173	0.216	0.271
4	0.086	0.114	0.153
5	0.044	0.061	0.088
6	0.023	0.034	0.051
7	0.014	0.020	0.031
8	0.009	0.013	0.020
9	0.007	0.009	0.013

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