NovoSeven® in the treatment of acquired hemophilia A: results from the ACQUI-7 prospective study in France

PO-W-4

A Borel-Derlon;[1] B Guillet;[2] A Aouba;[3] JY Borg;[4] JF Schved;[5] H Schneid;[6] B Villette;[6] H Lévesque[7]

[1]Hemophilia and von Willebrand Disease Center, University Hospital of Caen, Caen, France; [2]Hemophilia Treatment Center, University Hospital of Rennes and INSERM U1085, University of Rennes 1, Rennes, France; [3]Department of Internal Medicine, University Hospital of Caen, Caen, France; [4]Hemophilia Treatment Center, University Hospital of Rouen and INSERM CIC-CRB 0204, Rouen, France; [5]Regional Hemophilia Treatment Center, University Hospital St Eloi, Montpellier, France; [6]Medical Affairs Biopharm, Novo Nordisk, La Défense, France; [7]Department of Internal Medicine, INSERM U1096, IRIB, University Hospital of Rouen, Rouen, France

Objective

- To describe the use of recombinant factor VIIa (rFVIIa, NovoSeven®) in the hemostatic management of patients with acquired hemophilia A (AHA) in a real-world situation.

Conclusions

- The current data are in line with other European (EACH2[1], SACHA[2,3]) and US (HTRS[4]) published real-world data regarding effectiveness, dose, and duration of rFVIIa in AHA.
- The study provides additional information on the daily use of NovoSeven® in the treatment of AHA.

Introduction

- The efficacy and safety of recombinant factor VIIa (rFVIIa, NovoSeven®) in patients with acquired hemophilia A (AHA) are well established.
- However, there are limited data on the daily use of NovoSeven® in clinical practice for the treatment of bleeding episodes.
- The ACQUI-7 study was designed to give more practical data about the management of bleeding episodes with rFVIIa in patients with AHA, and to provide supporting evidence for the efficacy and safety of rFVIIa in this indication.[1]

Methods

- ACQUI-7 was a prospective, observational, multicenter study conducted in France.
- Patients were treated according to the investigator's judgment and the therapeutic practice at each of the 20 hospital sites involved.
- Participation in the study was not associated with any planned visit schedules or any dispensing of study medication.
- Male and female patients, recruited from December 2010 to December 2013, were included if they had anti-FVIII autoantibodies >1 Bethesda unit, FVIII activity <50%, and bleeding episodes treated with rFVIIa.
- Data collected were:
  - Patient characteristics, bleeding description (location and severity of bleed), description of rFVIIa therapy on the first five days (initial dose; frequency of administration; number of injections; total dose per day), total duration of treatment, total dose, and total number of injections.
  - Other hemostatic treatments were also reported (red blood cells; antifibrinolytic use).
- The statistical analysis was descriptive.

Results

Patient characteristics

- A total of 27 patients were treated with rFVIIa (Table 1).

Table 1 Demographics and patients characteristics.

Patients	(n=27)
Male gender, n (%)	18 (66.7)
Age (years), mean (±SD)	76.0 (±13.8)
Weight (kg), mean (±SD)	71.8 (±15.7)
CV disease and/or CV risk factor, n (%)	12 (44.4)
Age at AHA diagnosis (years), mean (±SD)	75.6 (±13.7)
Reason for diagnosis, n (%)	
Bleeding episode	25 (92.6)
Spontaneous	22 (88.0)
Surgery or traumatic	2 (8.0)
Both	1 (4.0)
Laboratory test	2 (7.4)
History of disease, n (%)	
Idiopathic AHA	16 (59.3)
Autoimmune pathology	6 (22.2)
Rheumatoid arthritis	5 (18.5)
Systemic lupus erythematosus	1 (3.7)
Malignancy (solid tumor/hematologic malignancy)	5 (18.5)
Previous bleeding before diagnosis[a], n (%)	9 (33.3)
Epistaxis/ecchymosis, n (%)	7 (25.9)
Days from first previous bleeding to final diagnosis, mean (±SD)	64.7 (±57.1)

AHA, acquired hemophilia A; CV, cardiovascular; SD, standard deviation.
[a]Previous bleeding ≥15 days before diagnosis and not the bleed leading to diagnosis.

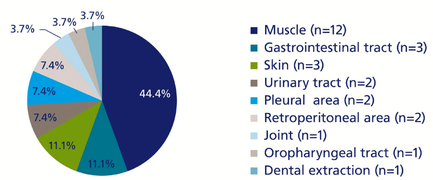
Bleeding episodes

- In 27 patients, 27 bleeding episodes were treated.
- Characteristics of the treated bleeding episodes are described by severity: severe (n=24, 88.9%) and nonsevere (n=3, 11.1%); and by location (Figure 1).

Treatment of bleeds with rFVIIa

- rFVIIa was initiated as first-line treatment for all patients.
- On Day 1 of treatment (median [Q1; Q3]):
  - Initial dose: 90.5 µg/kg [83.2; 100]
  - Number of doses: 2 [1.0; 4.0].
- Total treatment duration: 4 days [2; 11].
  - Nineteen patients (70.4%) were treated for up to 5 days.
- Total number of injections: 12 [5; 21].
- Cumulative dose: 0.90 mg/kg [0.48; 1.79].

Figure 1 Location of bleeding episodes (n=27).



- Table 2 describes rFVIIa use, Days 1–5, for severe bleeds.
- For the three nonsevere bleeds, the number of injections per day was similar to that for severe bleeds but total dose was half of that used for severe bleeds (data not shown).

Table 2 rFVIIa use from Days 1–5 for severe[a] bleeds (n=24).

Day of treatment	Number of injections, median [Q1; Q3]	Total dose (µg/kg/24 hours), median [Q1; Q3]
Day 1 (n=24)	2 [1.0; 4.5]	189 [97; 300]
Day 2 (n=22)	3 [2.0; 4.0]	255 [132; 333]
Day 3 (n=17)	3 [2.0; 4.0]	295 [162; 364]
Day 4 (n=14)	2 [2.0; 5.0]	200 [178; 423]
Day 5 (n=11)	3 [2.0; 6.0]	257 [171; 507]

[a]Severe: defined as life threatening, >1 red blood cell transfusion, hemoglobin level <2 g/dL, multiple bleeds location, diffuse ecchymosis, or other.

Associated hemostatic treatments

- In addition to rFVIIa treatment, 20 patients had at least one associated treatment: 74.1% had red blood cell transfusions (20/27); 11.1% were receiving antifibrinolytic treatment (3/27).

Efficacy

- Bleeds controlled: 24/27 (88.9%).
  - Severe bleeds controlled: 21/24 (87.5%).
  - The main reasons leading physicians to consider a controlled bleeding episode were described for 15 patients: the severity of bleeds decreased with or without total pain relief and/or hemoglobin level stabilization.
- Bleeds uncontrolled: 3/27 (11.1%).
  - Two patients were switched to another treatment: a patient with hemarthrosis at Day 2, and a patient with gastrointestinal bleeding at Day 20.
- Time from starting rFVIIa to cessation of bleeding episode, median [Q1; Q3]: 3 [1; 12] days.

Safety

- There were no serious adverse events related to rFVIIa, including thromboembolic events.
- Six deaths were reported, none related to rFVIIa:
  - One patient with sepsis (related to immunosuppressive treatment); two patients with general deterioration of health; two patients with malignant neoplasms; one patient treated with rFVIIa for 4 days who died 3 months later from bleeding (not treated).
  - All the deaths occurred at least a few months after cessation of rFVIIa treatment, with the exception of one patient with general health deterioration who died 12 days after the start of rFVIIa.

References

1. Tiede A, *et al. Blood Rev* 2015;29(Suppl 1):S19–S25.
2. Knoebl P, *et al. J Thromb Haemost* 2012;10:622–631.
3. Borg JY, *et al. Haemophilia* 2013;19:564–570.
4. Ma A, *et al. Blood Coagul Fibrinolysis* 2016; Epub.

Conflict of interest disclosure

AB-D, **BG**, **AA**, **JYB**, **JFS**, and **HL** have acted as consultants for Novo Nordisk. **HS** and **BV** are Novo Nordisk employees.

We thank all the participating investigators: F Bauduer, C Biron, A Borel-Derlon, L Bouillet, ME Briquel, D Christea, S Claeyssens, V Gay, S Girault, J Goudemand, B Guillet, Y Gruel, J Gutnecht, D Mallet, T Papo, P Roblot, F Sanderson, N Schleinitz, M Smahi, and F Volot. The authors acknowledge Benoît Huret, the project leader for ACQUI-7 (Novo Nordisk employee) and the medical writing assistance of Anna Binks (PAREXEL), funded by Novo Nordisk.

Presented at the World Federation of Hemophilia (WFH) World Congress, July 24–28, 2016, Orlando, FL, USA.