La scelta del concentrato puro di Fattore von Willebrand

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FVIII/VWF concentrates

- Several plasma-derived concentrates are available
- Differ in terms of :
  - method of purification and method of viral inactivation
  - VWF:Rco/FVIII ratios

Table 5 FVIII/von Willebrand factor (VWF) concentrates and recombinant VWF (rVWF) for the treatment of von Willebrand disease [54,58]

Product	Purification	Viral inactivation	VWF:RCo/ FVIII ratio
Human plasma-derived FVIII/VWF concentrates			
Factor 8Y (Bio Products Laboratory)	Heparin/glycin precipitation	Dry heat (80 °C, 72 h)	0.81
Fanhdi/Alphanate (Grifols)	Heparin ligand chromatography	Solvent/detergent and dry heat (80 °C, 72 h)	1.04
Haemate-P/Humate-P (CSLBehring)	Multiple precipitation	Pasteurization (60 °C, 10 h)	2.4
Immunate (Baxalta)	Ion exchange chromatography	Solvent/detergent and vapor heat (60 °C, 10 h)	1.1
Wilate (Octapharma)	Ion exchange + size exclusion	Solvent/detergent and dry heat (100 °C, 2 h)	1

(Peyvandi F et al J Thromb Haemost 2016; DOI: 10.1111/jth.13491)

FVIII/VWF concentrates

- After infusion of plasma-derived concentrates, the levels of both VWF and FVIII increased
- However, the FVIII levels may rise higher than desired due to:
  - stabilization of endogenous FVIII by the infused VWF
  - higher concentrations of FVIII in some VWF concentrates
- This can produce an increased risk of thrombosis, especially in elderly patients and during surgical procedures

(Mannucci et al Blood 2002; 99:450-456; Koster T et al The Lancet 1995; 345:152-155)

Pure VWF concentrates

- One plasma-derived with a very small amount of FVIII (VWF:RCo/FVIII ratio of ~50) (not licensed in the USA and Canada)
- Recombinant VWF (rVWF, vonicog alfa, Vonvendi), with complete absence of FVIII
- Recommended in patients with normal FVIII levels or in those with a high thrombotic risk

Table 5 FVIII/von Willebrand factor (VWF) concentrates and recombinant VWF (rVWF) for the treatment of von Willebrand disease [54,58]

Product	Purification	Viral inactivation	VWF:RCo/ FVIII ratio
Human plasma-derived			
Wilfactin/Wilfact (LFB)	Ion exchange + affinity chromatography	Solvent/detergent and 35-nm filtration, dry heat (80 °C, 72 h)	~ 50
rVWF			
Vonvendi (Baxalta)	Ion exchange + affinity chromatography	Solvent/detergent ultrafiltration	NA

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Use of Wilfactin in prophylaxis
Case report

Clinical data

- Male, 85 years
- Co-morbidities:
  - Paget disease (1990)
  - hypertension (1998)
  - MGUS
  - Liver cirrhosis
  - Mild renal chronic disease

- Bleeding history **before** diagnosis:
    - Epistaxis
    - Minor bleeding after tooth avulsion and tonsillectomy

Laboratory data
Diagnosis

- Factors levels at diagnosis:

FVIII:C	28%
VWF:Ag	27%
VWF:RCo	<5%
Loss of high molecular weight multimers	

- Diagnosis: **VWD Type 2A** in 1973 (43 years)

Laboratory history

- Progressive increase of FVIII:C and VWF:RCo
  - 2004: FVIII:C 75% VWF:Ag 55% VWF:RCo 6%
  - 2009: FVIII:C 105% VWF:Ag 60% VWF:RCo 6%
  - 2011: FVIII:C 97% VWF:Ag 86% VWF:RCo 14%

Bleeding history (after diagnosis)

- Gastro-intestinal bleedings
  - 1982 associated with ileocecal stenosis → hemicolectomy
  - 1990-1991 (RBC: 13 units), 1993 (RBC: 2 units), 1994 (RBC: 4 units), 1999 (RBC: 25 units)
  - 2000, associated with arterovenous malformation (RBC: 43 units) → surgery
  - 2004, associated with rectal arterovenous malformation (RBC: 8 units)
  - 2005 (RBC: 5 units), 2007 (RBC: 5 units), 2009 (RBC: 9 units)
  - 2010, 2011, 2012 (RBC: 2 units)

- Patient had been treated on demand with FVIII/VWF concentrate until 2013

After starting with Wilfactin

- 2013: gastro-intestinal bleeding (gastric and colon arterovenous malformations) → Argon Plasma Coagulation (APC) and treatment with Wilfactin (4 infusions)

- October **2013**: patient started **prophylaxis** with Wilfactin (1000U per infusion, 2-3 per week), but it was **stopped** due to venous access

- March **2014**: port-a-cath implantation and **starting of regular prophylaxis** with Wilfactin (1000U, 3 times per week)

Clinical and laboratory data during prophylaxis

FVIII:C	78%	→	81%
VWF:Ag	169%	→	212%
VWF:RCo	36%	→	55%

- After the start of prophylaxis: Gastro-intestinal bleeds → 6 different episodes from october 2014 to february 2016 (blood transfusion in 2 episodes)

- After 2-3 years of prophylaxis our patient stopped to have GI bleeding and did not require any blood transfusion in the last 6 months (effect of VWF on angiogenesis?)

Why Wilfactin?

- Normalization of FVIII:C due to age and cirrhosis
- No need to use the concentrate in association with any FVIII product (normal levels of FVIII)

Use of Wilfactin in surgery
Case report

Clinical and laboratory data

- Male, 56 years
- Bleeding history **before** diagnosis:

  - Epistaxis

  - Easy bruising

  - Gastointestinal bleeding (hemorrhagic gastritis) at 10 years old, treated with blood transfusion

Historical values:

FVIII:C	28%
VWF:Ag	27%
VWF:RCo	<5%

- Diagnosis: **VWD Type 2A** in 1972 (12 years)

Bleeding history (after diagnosis)

- Nose bleeding epistaxis treated with package, antifibrinolytic, DDAVP, cryoprecipitate, and with FVIII/VWF complex (Fanhdi)
- Two tooth extractions performed with DDAVP
- Tooth abscess with bleeding treated with DDAVP

- **DDAVP test** in 2006:

	Basal	1 hour	2 hours	4 hours
FVIII:C	34%	111%	95%	73%
VWF:Ag	13%	26%	20%	20%
VWF:RCo	<6%	<6%		

Clinical/Laboratory history

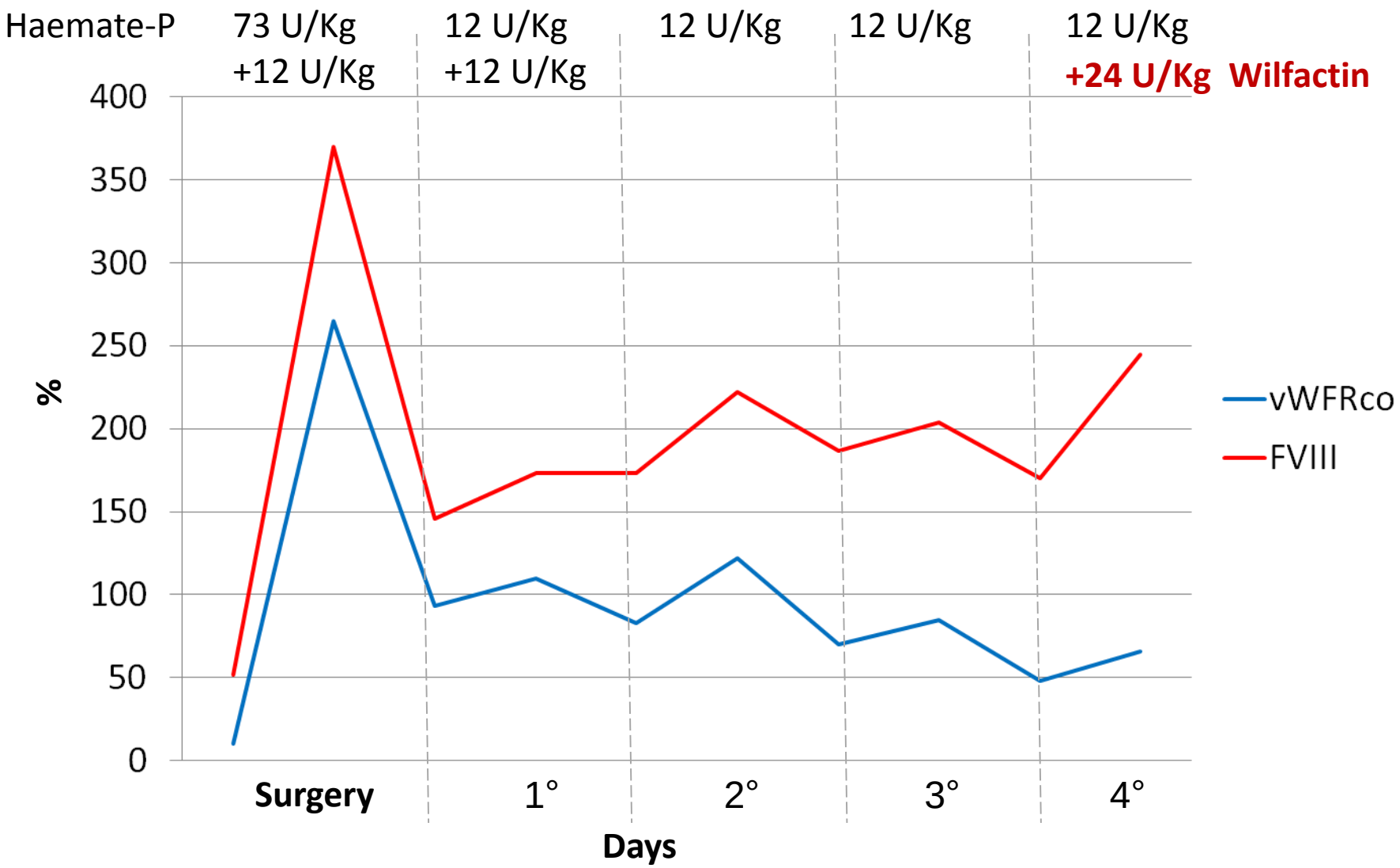
- Co-morbidities:
  - Hypertension therapy
  - Gastroesophageal reflux (MRGE)
  - Previous HCV infection eradicated in 2006

- Current levels of FVIII:C and VWF:RCo

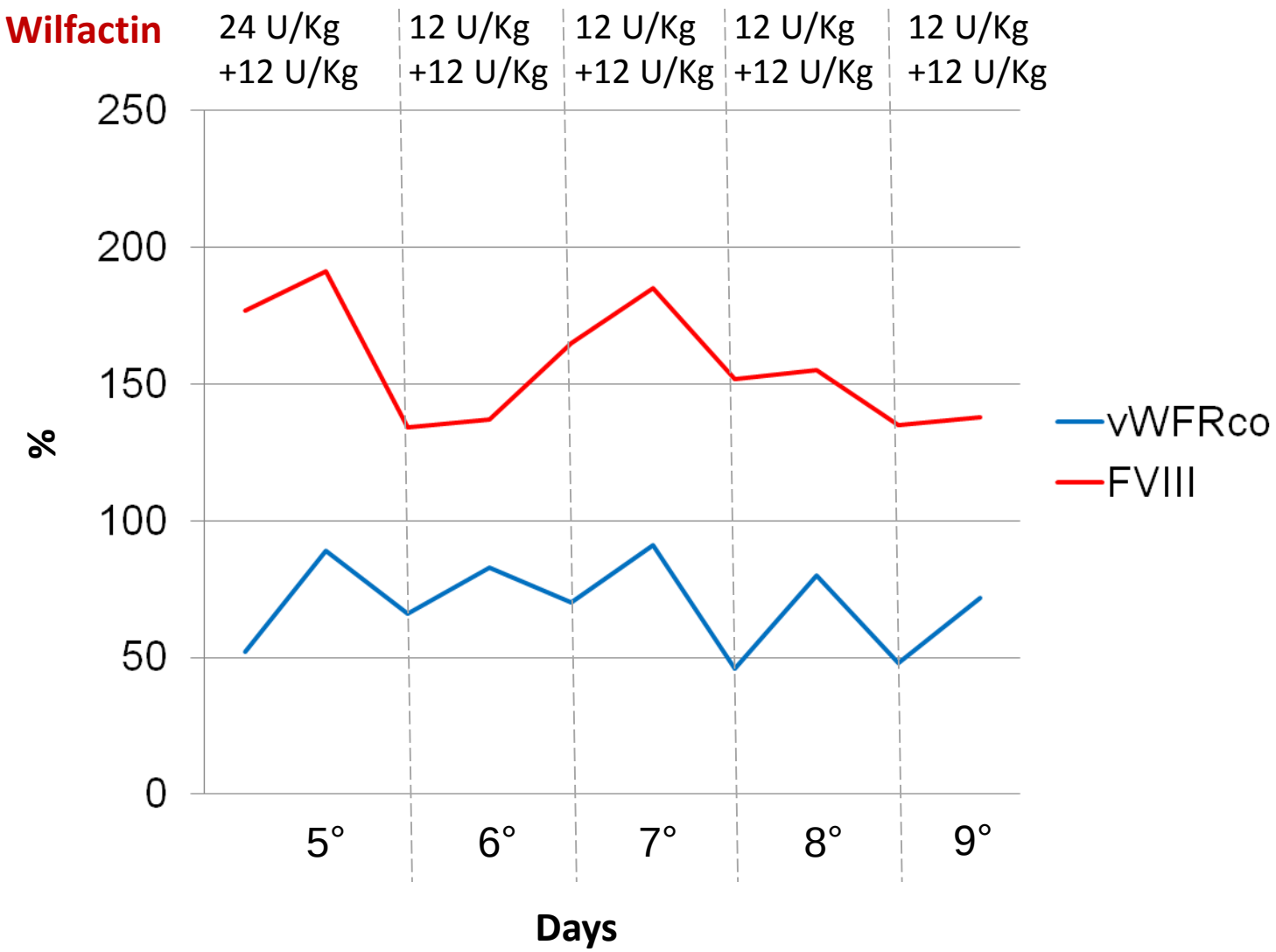
- FVIII:C	52%
- VWF:Ag	17%
- VWF:RCo	10%

Surgery (1)

Partial nephrectomy – Weight 82kg



Surgery (2)


Wilfactin
24 U/Kg +12 U/Kg
12 U/Kg +12 U/Kg
12 U/Kg +12 U/Kg
12 U/Kg +12 U/Kg
12 U/Kg +12 U/Kg
250
200
150
100
50
0
%
5°
6°
7°
8°
9°
Days
vWFRco
FVIII

Conclusion

- The advantage of pure VWF is to limit the FVIII increase that occurs after repeated infusions
- High FVIII:C concentrates are unnecessary and perhaps dangerous increasing increses the risk of thrombosis
- The delayed increase in FVIII observed with the VWF concentrate has to be dealt with when prompt hemostasis is required particularly in patients with severe VWD and low basleine FVIII levels