Nuove molecole per il trattamento dell'emofilia

Angiola Rocino

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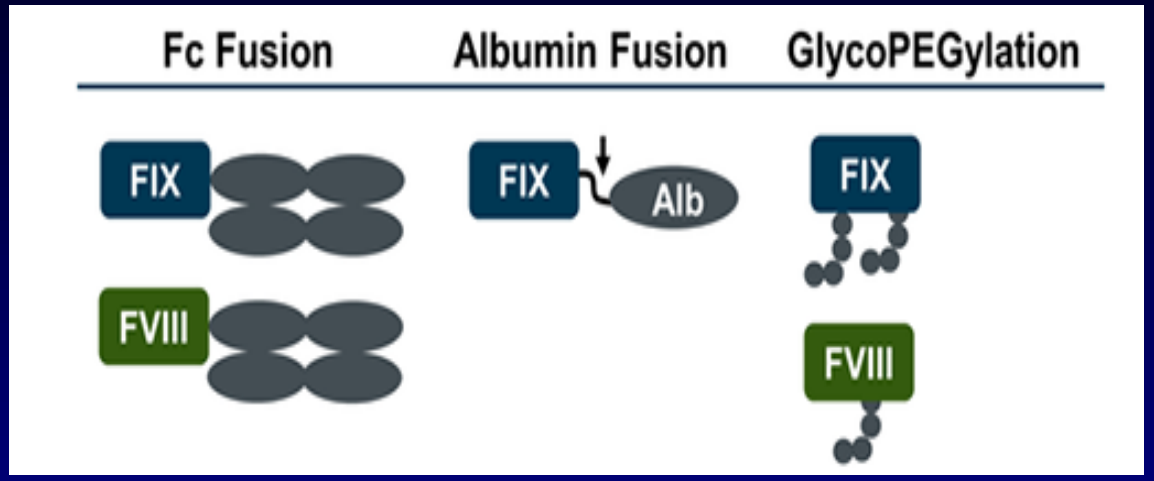
Napoli

Abano Terme 10 novembre 2016

Disclosures of Angiola Rocino

Consultant to Bayer, Baxter, Baxalta, Baxata part of Shire, CSL Behring, NovoNordisk, Octapharma, Pfizer, Sobi.

Sviluppo di nuove molecole di FVIII e FIX a più lunga emivita: Partners



Fusione con albumina umana ricombinante. Solo FIX

rFIX-FP (Idelvion®)

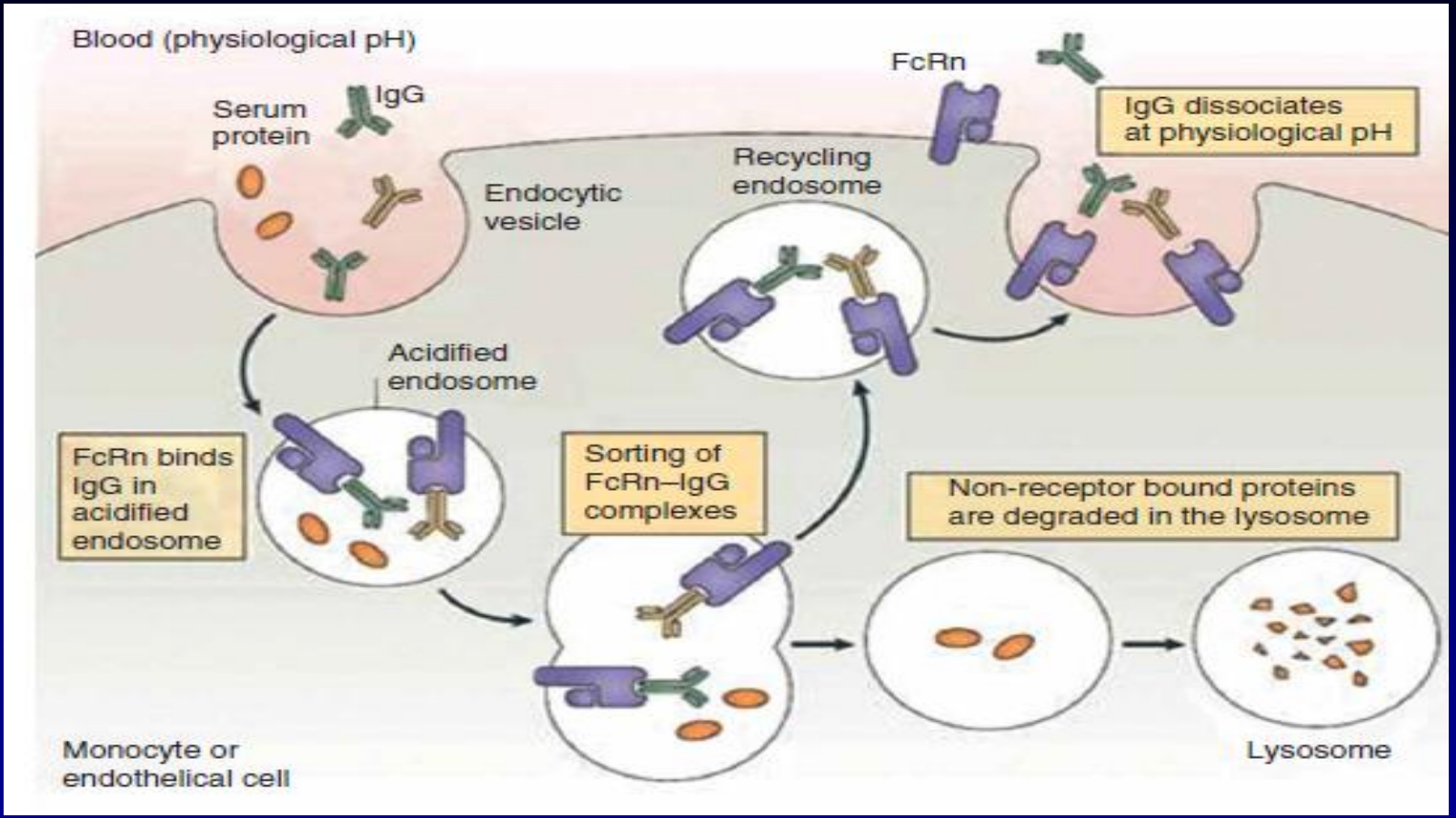
Fusione con Fc domain delle IgG:

rFVIII-Fc (Elocta®); rFIX-Fc (Alprolix®)

Aggiunta di polietilen glicol (PEG) catene di 5-60 kDa:

BAX 855 (Adynovate®), Bay 94-9027, N8-GP

FcRn recycling pathway



IgG si lega al recettore Fc neonatale (FcRn); ciò protegge la proteina di fusione (FVIII/FIX) dalla degradazione lisosomiale e ne consente il riciclo con reimmissione in circolo. Lo stesso meccanismo viene attuato in caso di fusione con albumina.

The use of enhanced half-life coagulation factor concentrates in routine clinical practice: guidance from UKHCDO

P. COLLINS,* E. CHALMERS,† P. CHOWDARY,‡ D. KEELING,§ M. MATHIAS,¶ J. O'DONNELL,** K. J. PASI,†† S. RANGARAJAN‡‡ and A. THOMAS§§

Haemophilia 2016; 22:487-98

FVIII – prodotti con Enhanced half-life (EHL)

Product	Company	Cell line	Biochemical strategy	Age (years)	Subjects	Incremental recovery (IU dL^{-1})/(IU kg^{-1})	Half-life (h)
rFVIII-Fc	Sobi	HEK293H	B-domain-deleted rFVIII fused with human IgG_1 Fc domain	≥12	15	Mean (95% CI) 1.83 (1.6–2.1)	Mean (95% CI) 18.8 (14.3–24.5)
				≥12	28	Mean 2.2	Mean 19
				6–<12	31	Mean (95% CI) 2.44 (2.07–2.80)	Mean (95% CI) 14.9 (12–17.8)
				<6	23	Mean (95% CI) 1.92 (1.8–2.0)	Mean (95% CI) 12.7 (11.2–14.1)
Bax 855	Baxalta	CHO	Full-length rFVIII with lysine PEGylation (20 kDa PEG ×2)	12–65	26	Mean (SD) 2.49 (0.69)	Mean (SD) 14.3 (3.8)
Bay 94-9027	Bayer Healthcare	BHK	B-domain-deleted rFVIII with site-specific PEGylation (single 60 kDa PEG)	≥18	14	Mean (range) 2.9 (2.1–4.1)	Mean (range) 18.2 (13.7–28.1)
N8-GP	Novo-Nordisk	CHO	B-domain-truncated rFVIII with site-specific PEGylation (single 40 kDa PEG)	≥18	26	Mean (SD) 2.4 (0.6)	Mean (SD) 19 (5.53)

Efraloctocogalfa, ELOCTA®

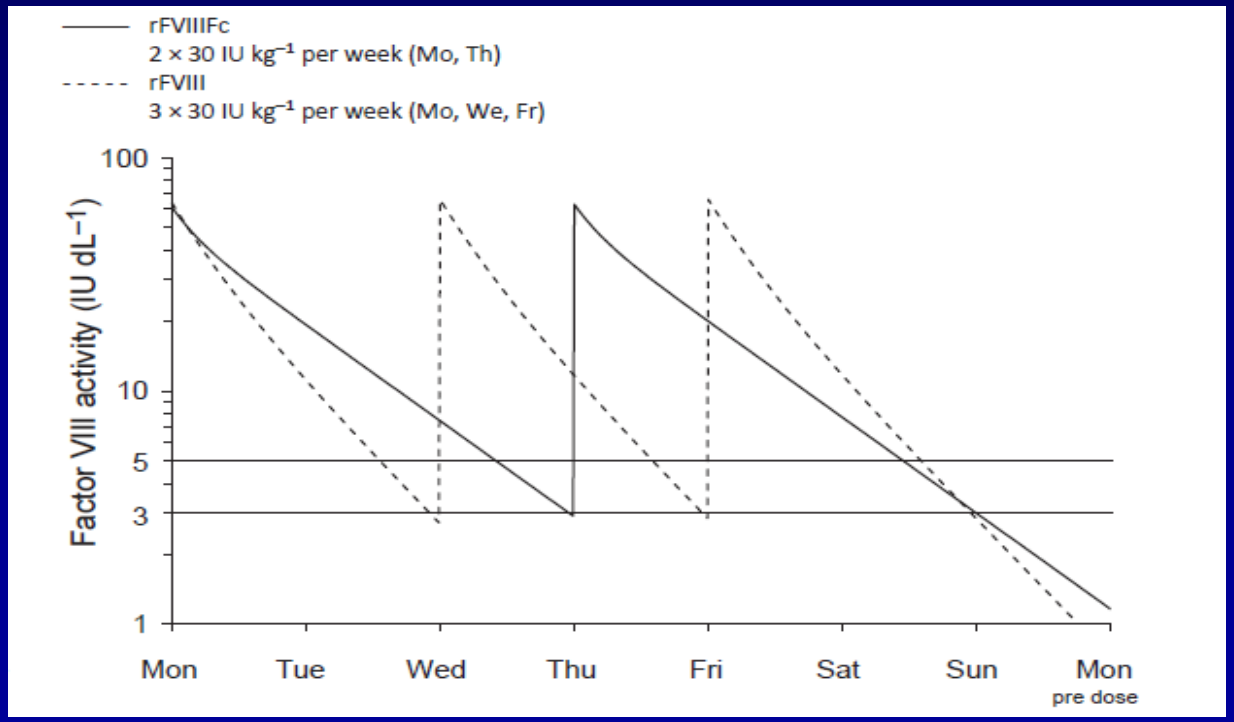
Incremento half-life: 1.5-1.7

FVIII-Fc:

Dosing regimens, FVIII levels and estimated haemostatic protection with special focus on rFVIIIFc

E. BERNTORP,* C. NEGRIER,† P. GOZZI,‡ P-M. BLAAS‡ and S. LETHAGEN‡§

Factor	Injections/week	Dose (IU/kg/week)	Peak (IU/dL)	Troughs (IU/dL)	Time below 5 IU/dL/week (days)	Time below 3 IU/dL/week (days)	Time below 1 IU/dL/week (days)
rFVIIIFc	2	60	62	3.0/1.2	2.1	1.0	0
rFVIII	3	90	65	2.7/2.8/0.7	2.3	1.2	0.2



Similar factor levels with same dose per injection and one injection less per week.

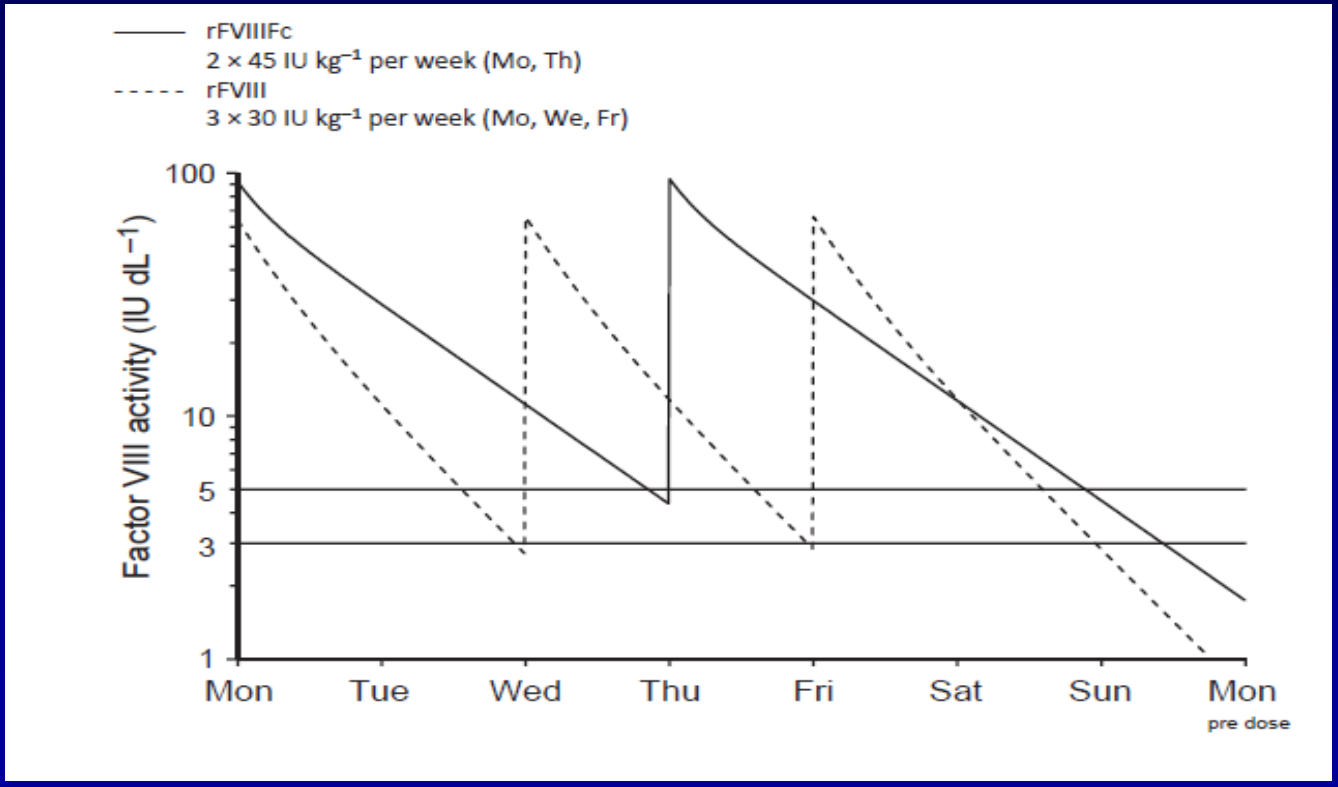
Haemophilia, 2016

FVIII-Fc:

Dosing regimens, FVIII levels and estimated haemostatic protection with special focus on rFVIIIFc

E. BERNTORP,* C. NEGRIER,† P. GOZZI,‡ P-M. BLAAS‡ and S. LETHAGEN‡§

Factor	Injections/week	Dose (IU/kg/week)	Peak (IU/dL)	Troughs (IU/dL)	Time below 5 IU/dL/week (days)	Time below 3 IU/dL/week (days)	Time below 1 IU/dL/week (days)
rFVIIIFc	2	90	93	4.4/1.7	1.3	0.6	0
rFVIII	3	90	65	2.7/2.8/0.7	2.3	1.2	0.2



Higher factor levels with same weekly factor consumption and one less injection .

Haemophilia, 2016

FIX – prodotti ad Enhanced half-life (EHL)

Table 2. Enhanced half-life factor IX products: manufacturing characteristics and pharmacokinetics.

Product	Company	Cell line	Biochemical strategy	Age	Subjects	Incremental recovery (IU dL^{-1})/(IU kg^{-1})	Half-life (h)
N9-GP	Novo-Nordisk	CHO	rFIX with site-specific PEGylation (single 40 kDa PEG)	12–65	15	Mean (SD) 1.4 (0.4)	Mean (SD) 96 (42)
				12–65	30	Mean (CV) 2.0 (14.5)	Mean (CV) 93 (19.5)
				≥6–<12	13	Mean 1.6	Mean 76.3
				<6	12	Mean 1.5	Mean 69.6
rFIX-Fc Alprolix	Sobi	HEK293H	rFIX fused with IgG_1 Fc	≥18	11	Mean (range) 0.87 (0.63–1.2)	Mean (range) 57.6 (47.9–67.2)
				≥12	22	Mean (95% CI) 0.92 (0.77–1.1)	Mean (95% CI) 82.1 (71.4–94.5)
				≥6–<12	13	Mean (95% CI) 0.72 (0.61–0.84)	Mean (95% CI) 70.3 (61.0–81.2)
				Median (range) 8 (6–11)			
				<6	11	Mean (95% CI) 0.59 (0.52–0.68)	Mean (95% CI) 66.5 (55.9–79.1)
				Median (range) 2 (1–4)			
rFIX-FP	CSL Behring	CHO	rFIX fused with recombinant human albumin	12–65	28	Mean (SD) 1.4 (0.28)	Mean (SD) 91.6 (20.7)
				12–65	15	Mean 1.5	Mean 94.8
				≥6–<12	15	Mean (SD) 1.06 (0.239)	Mean (SD) 92.8 (19)
				<6	12	Mean (SD) 0.95 (0.20)	Mean (SD) 89.6 (11.2)

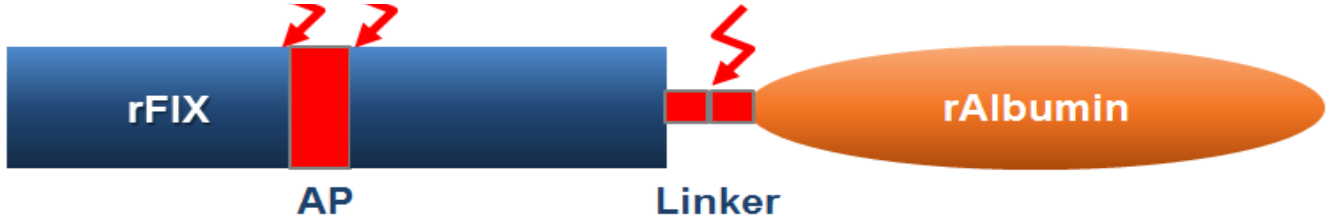
Incremento half-life a 60-90 ore

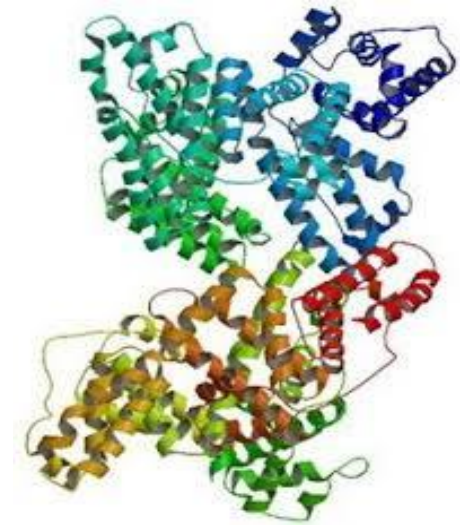
IDELVION®

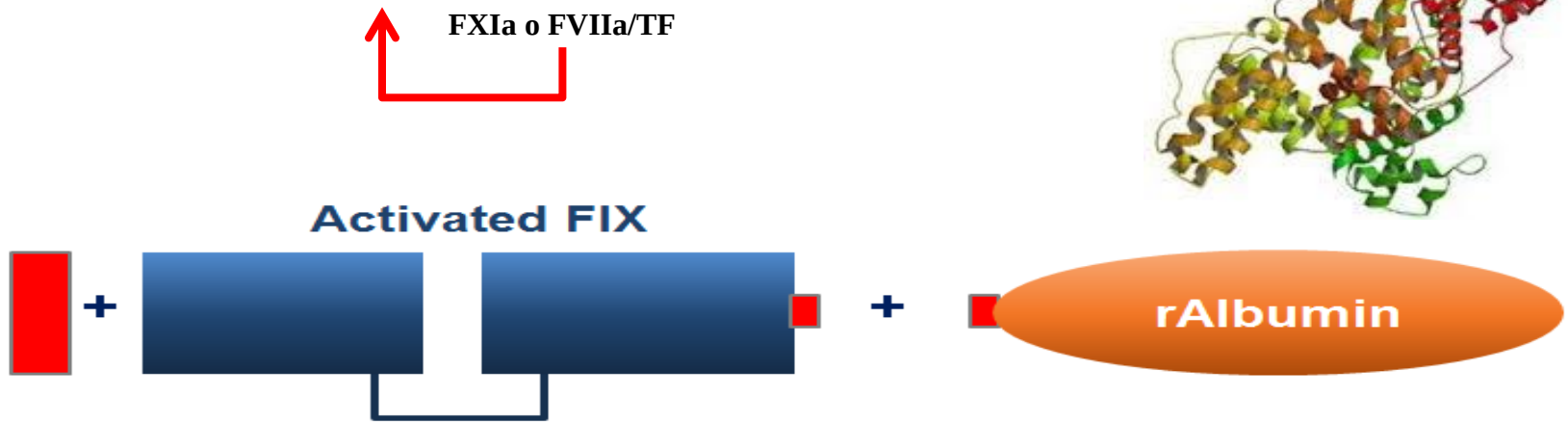
Haemophilia 2016; 22:487-98

rIX-FP – disegno della molecola

Breve linker clivabile, derivato dal peptide di attivazione del FIX nativo





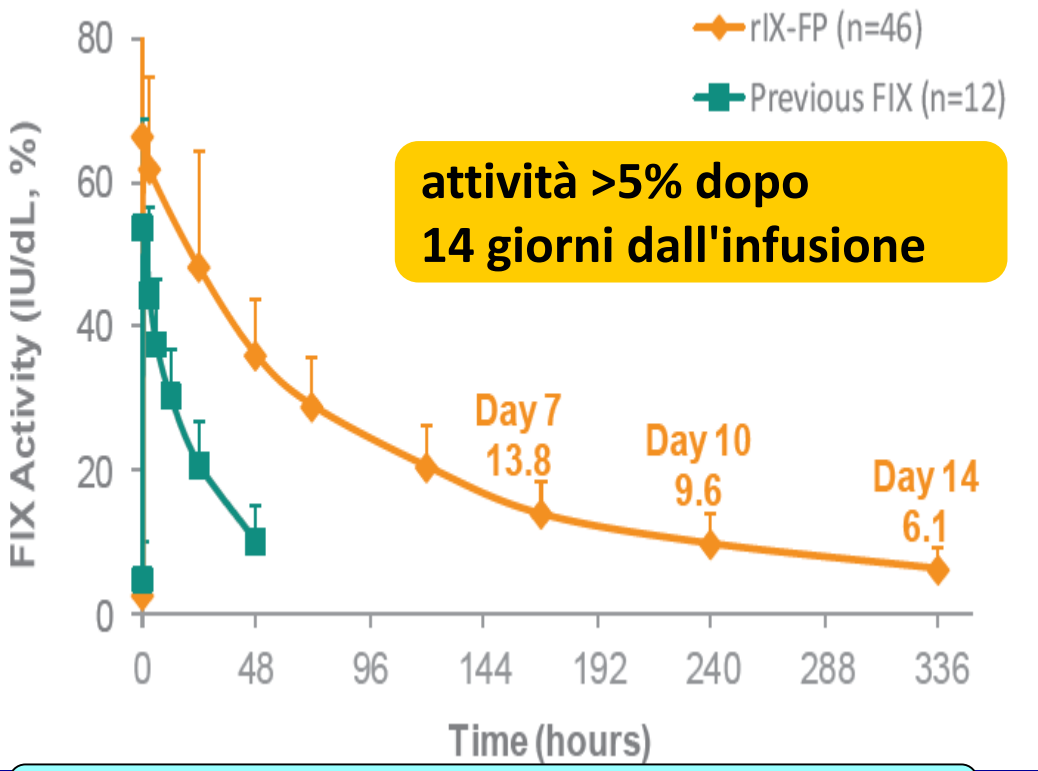


rIX-FP rimane intatto in circolo finchè non è attivato e rAlb viene rimossa da rFVIIa/TF o FXIa

AP, activation peptide; CHO, Chinese hamster ovary.
Metzner HJ *et al*. *Thromb Haemost* 2009 Oct;102(4):634-44. 2. Schulte S. *Thromb Res* 2009 Dec;124 Suppl 2:S6-8.

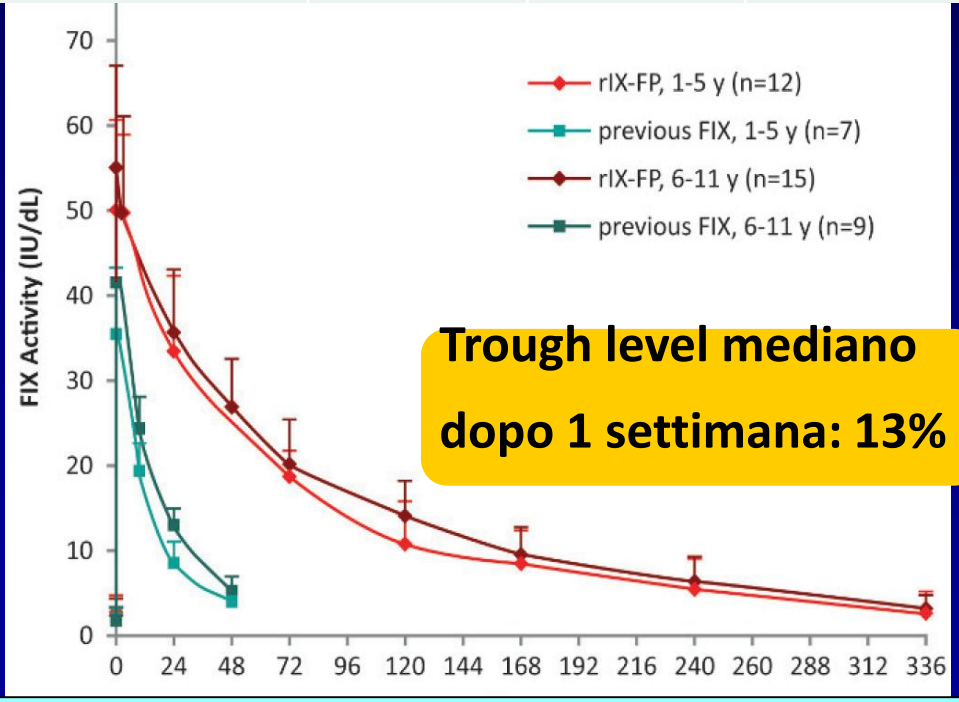
Fase II/III – Adolescenti-adulti (12-65 anni)
Fase III – Pazienti pediatrici (1-11 anni): attività FIX e PK

Mean (50 IU/kg)	rIX-FP (n=46)	rFIX (n=8)	rIX-FP/ rFIX ratio
IR (IU/dL)/(IU/kg)	1.27	0.834	1.5
$AUC_{0-\infty}$ (IU·h/dL)	7,176	1,396	5.1
$t_{1/2}$ (h)	101.7	24.2	4.2
CL (mL/kg/h)	0.769	4.03	0.19



Santagostino et al., Blood 2016;127:1761-9

<12 years 50 IU/kg*	rIX-FP (n=27)	Previous FIX (n=17)	rIX-FP/ previous FIX ratio
IR (IU/dL)/(IU/kg)	1.01	0.74	1.36
$AUC_{0-\infty}$ (IU·h/dL)	4,894	888	5.5
$t_{1/2}$ (h)	91.4	18.6	4.9
CL (mL/kg/h)	1.11	6.40	0.17



Kenet et al., Thromb Haemost 2016; 116:659-68

rFIX – FP: Profilassi settimanale

AsBR mediano pari a **zero**

	Adults	Paediatric patients		
	Age 12–65 years (n=40)	Age 1–11 years (n=27)	Age 1–5 years (n=12)	Age 6–11 years (n=15)
ABR				
Spontaneous, median (IQR)	0.00 (0.00, 0.00)	0.00 (0.00, 0.91)	0.00 (0.00, 0.10)	0.78 (0.00, 1.99)
Total joint, median (IQR)	0.00 (0.00, 1.53)	0.99 (0.00, 2.33)	0.50 (0.00, 1.45)	1.13 (0.00, 2.36)
Total, median (IQR)	0.00 (0.00, 1.87)	3.12 (0.91, 5.91)*	2.64 (2.00, 6.48)*	3.39 (0.76, 5.91)*
Prophylaxis dose, median (IQR) [IU/kg]	40 (37, 50)**	45.7 (40.6, 55.8)	48.7 (44.8, 56.2)	42.6 (40.4, 51.0)

Consumo di UI di FIX significativamente inferiore *vs* precedente (50%)

Kenet G, et al., Thromb Haemost 2016; Santagostino et al, Blood 2016

Quali prospettive da disponibilità di prodotti a Enhanced half-life (EHL) ?

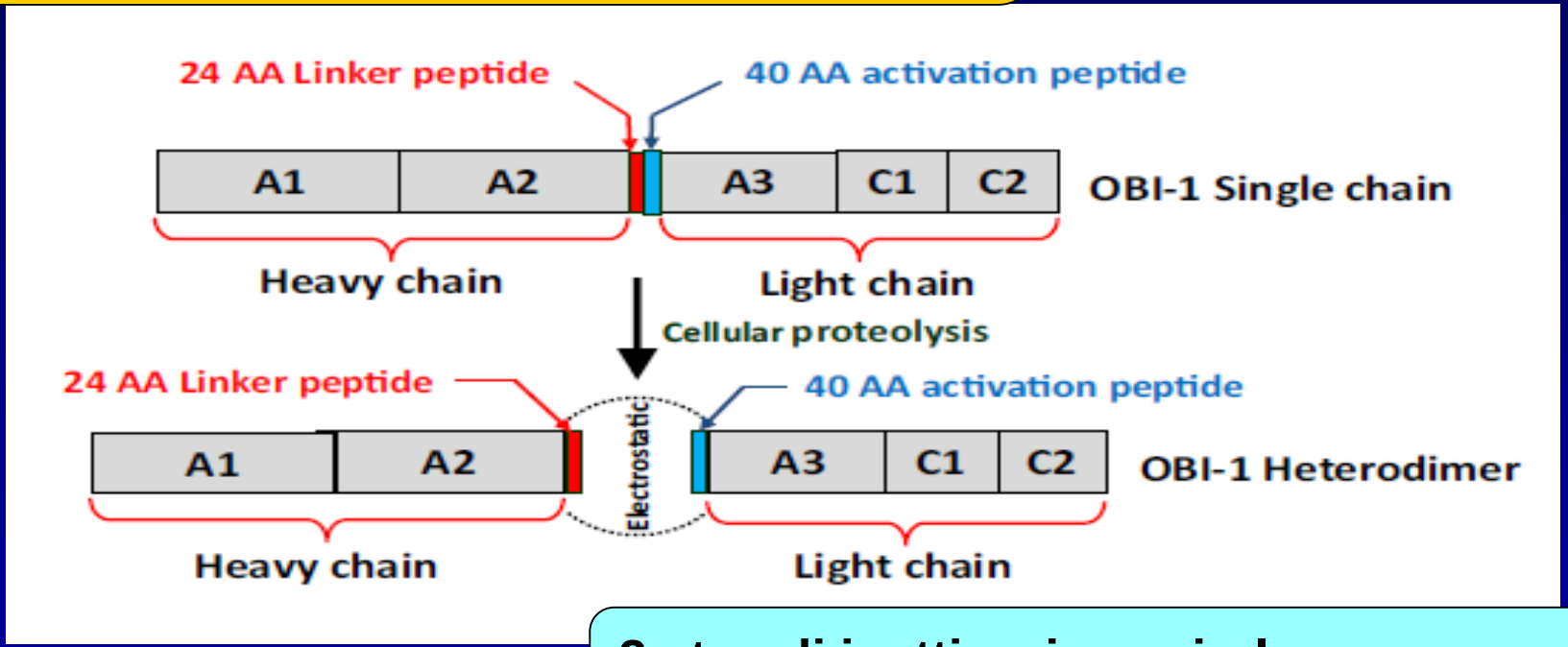
Profilassi in tutti i pazienti con emofilia grave con maggiore flessibilità nella scelta del regime di trattamento.
Maggiore individualizzazione sulla base di fenotipo emorragico (ABR, AJBR) e esigenze personali del paziente.

Porcine recombinant factor VIII (Obizur; OBI-1; BAX801): product characteristics and preclinical profile

D. LILLICRAP,* A. SCHIVIZ,† C. APOSTOL,† P. WOJCIECHOWSKI,‡ F. HORLING,† C. K. LAI,‡ C. PISKERNIK,† W. HOELLRIEGL† and P. LOLLAR§

Haemophilia 2016; 22:308-17

B-domain deleted rpFVIII prodotto in cellule BHK geneticamente modificate (Susoctocog alfa)



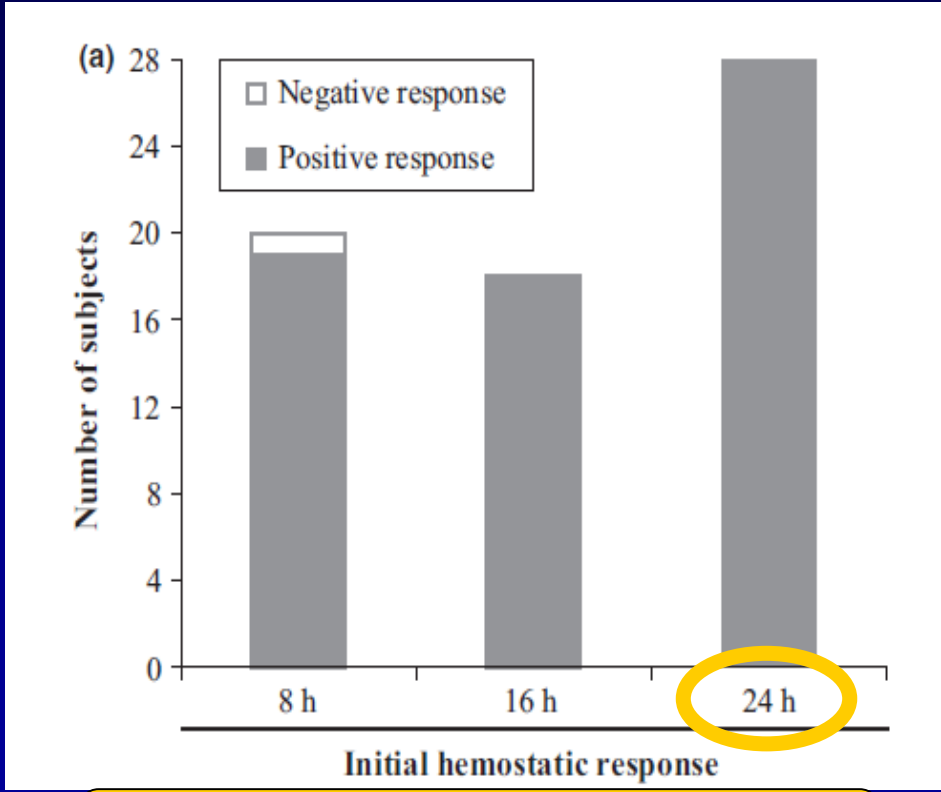
2 step di inattivazione virale: solvente/detergente + nanofiltrazione (15 nm)

Efficacy and safety of OBI-1, an antihaemophilic factor VIII (recombinant), porcine sequence, in subjects with acquired haemophilia A

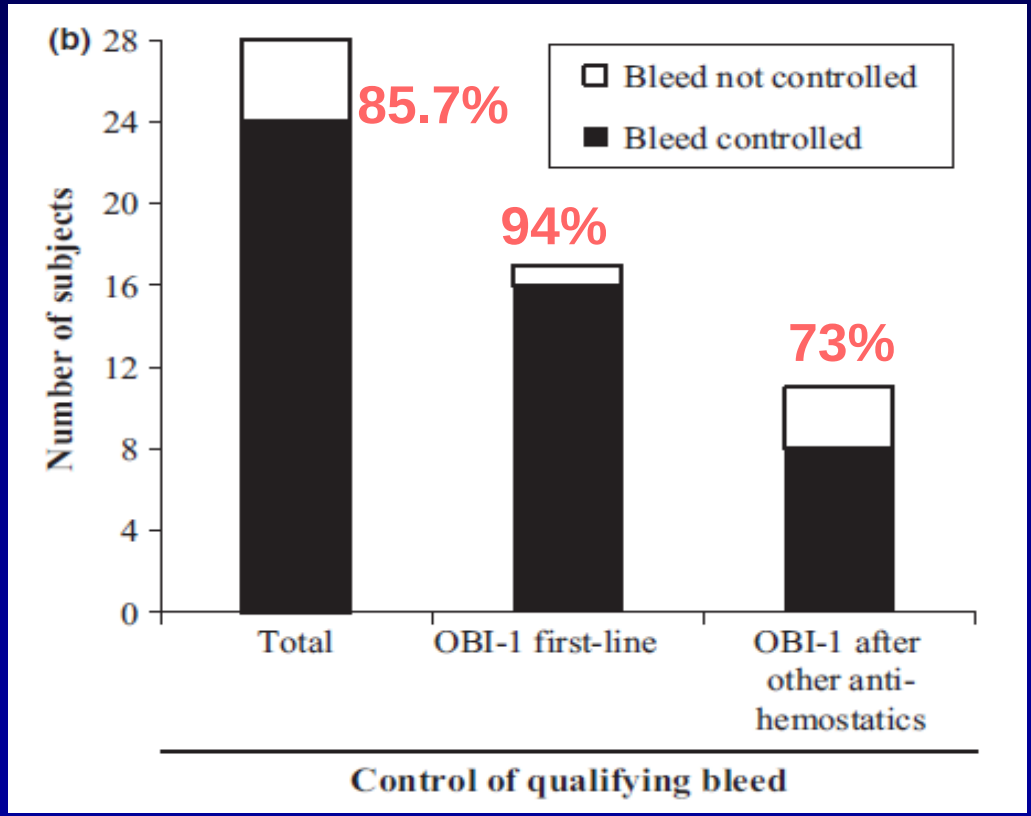
R. KRUSE-JARRES,* J. ST-LOUIS,† A. GREIST,‡ A. SHAPIRO,‡ H. SMITH,§ P. CHOWDARY,¶ A. DREBES,¶ E. GOMPERTS,** C. BOURGEOIS,†† M. MO,‡‡ A. NOVACK,‡‡ H. FARIN‡‡ and B. EWENSTEIN‡‡

Haemophilia 2015; 21:162–170

29 pazienti: 19 maschi, 10 donne; età mediana: 70 anni.



Dose iniziale fissa: 200 UI/kg



Recombinant porcine sequence factor VIII (rpFVIII) for acquired haemophilia A: practical clinical experience of its use in seven patients

M. D. TARANTINO,* A. CUKER,† B. HARDESTY,‡ J. C. ROBERTS* and M. SHOLZBERG§

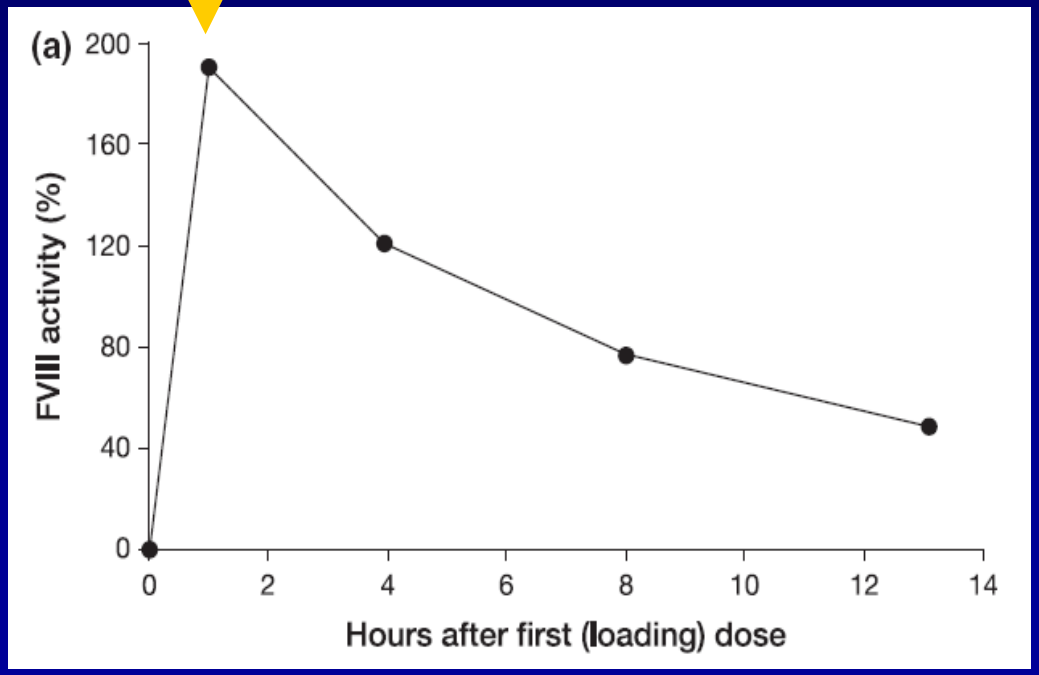
Haemophilia, 2016

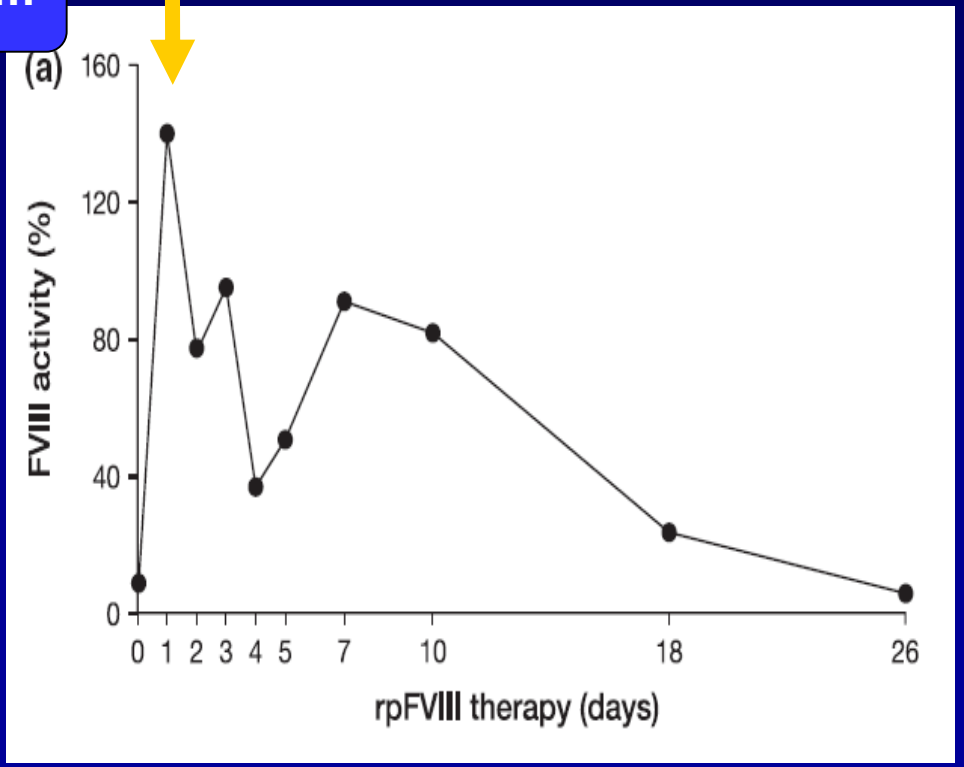
Case series, 7 pazienti di età mediana: 78 anni.

100 IU/kg

Un caso di AHA post-partum

100 IU/kg/day





Superare le difficoltà di gestione delle emorragie in pazienti con AHA: le raccomandazioni potranno subire variazioni

Prescrivibile in Italia in base alla legge n. 648 del 1996*. 648[28].

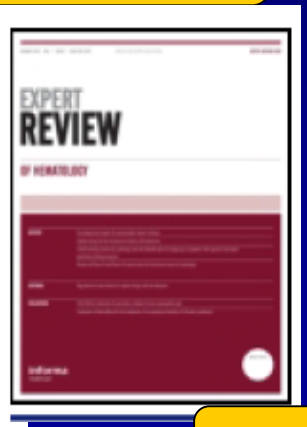
Porcine recombinant factor VIII: an additional weapon to handle anti-factor VIII antibodies

Pier Mannuccio Mannucci[1], Massimo Franchini[2]

Blood Transfus **DOI 10.2450/2016.0030-16**

Recombinant B domain deleted porcine factor VIII for the treatment of bleeding episodes in adults with acquired hemophilia A

Edward Gomperts



8:427-432

*Determina n. 1078/2015. Gazzetta Ufficiale della Repubblica Italiana, Serie Generale n. 188, 14-8-2015

Innovative Pharmacological Therapies for the Hemophilias Not Based on Deficient Factor Replacement

Semin Thromb Hemost 2016; 42:526-32

Pier Mannuccio Mannucci, MD[1] Maria Elisa Mancuso, MD, PhD[1] Elena Santagostino, MD, PhD[1]
Massimo Franchini, MD[2]

AGENTI BYPASSANTI:
rFVIIa – FP
ACE910

Inibitori degli Anticoagulant Pathways:
Anti-TFPI (Concizumab)
Inibitore della sintesi di AT (ALN-AT3)

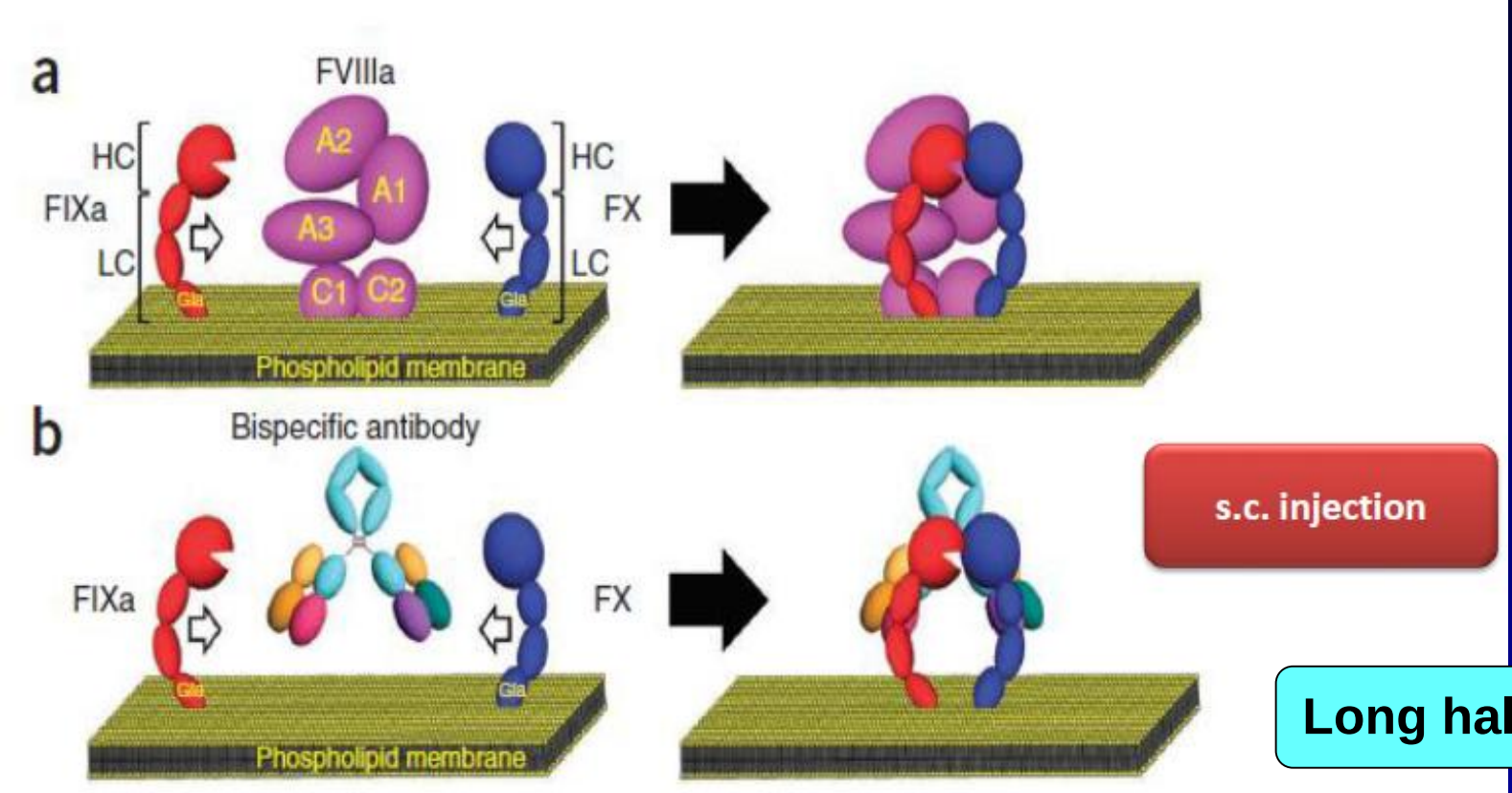
Aumento dell'attività di fattori della coagulazione:
Super-FVa
FXa variant

Stabillizzazione del coagulo: FXIII

Product	Company	Technology	Stage of development	Main characteristics
rFVIIa-FP	CSL Behring (Marburg, Germany)	Fusion protein with albumin	Phase II/III study ongoing	Prolonged half-life (8.5 h)
ACE910	Chugai Pharmaceuticals/La Roche Hoffman (Tokyo, Japan)	Chimeric bispecific humanized antibody	Phase I study ongoing (interim analysis published)	Prolonged half-life (2 wk) SC weekly administration reduced ABR in hemophiliacs
Concizumab	Novo Nordisk (Bagsvaerd, Denmark)	Humanized monoclonal antibody	Phase I studies (Explorer 1–3)	Prolonged half-life (31.1–74.2 h) SC or IV administration improved thrombin generation and reduced TFPI levels for ≥ 14 d in hemophiliacs
ALN-AT3	Alnylam Pharmaceuticals (Cambridge, MA)	siRNA	Phase I study (interim analysis published)	SC administration improved thrombin generation, whole blood clot formation, and reduced antithrombin levels to 20% in hemophilia patients
^{super}FVa	–	Bioengineered FVa variant	Preclinical phase	Increased thrombin generation in acquired hemophilia models Synergistic effect with rFVIIa
FXa^{I16L}	–	Bioengineered zymogen-like FXa variant	Preclinical phase	Longer lasting plasma activity than wild-type FXa (60 min Vs. 1 min) Increased thrombin generation in hemophilia models
FXIII	CSL Behring (Marburg, Germany)	Plasma-derived product	Preclinical phase	Long half-life (9 d) Improve clot stability alone or in association with rFVIIa

Mannucci PM et al. Semin Thromb Hemost 2016; 42:526-32

ACE910 (emicizumab): anti- FIXa/FX bispecific antibody (FVIII mimetic agent)



Muto A et al. J Thromb Haemost 2014; 12: 206-13
Muto A et al. Blood 2014; 124: 3165-71
Shima M et al. NEJM 2016; 374: 2044-53

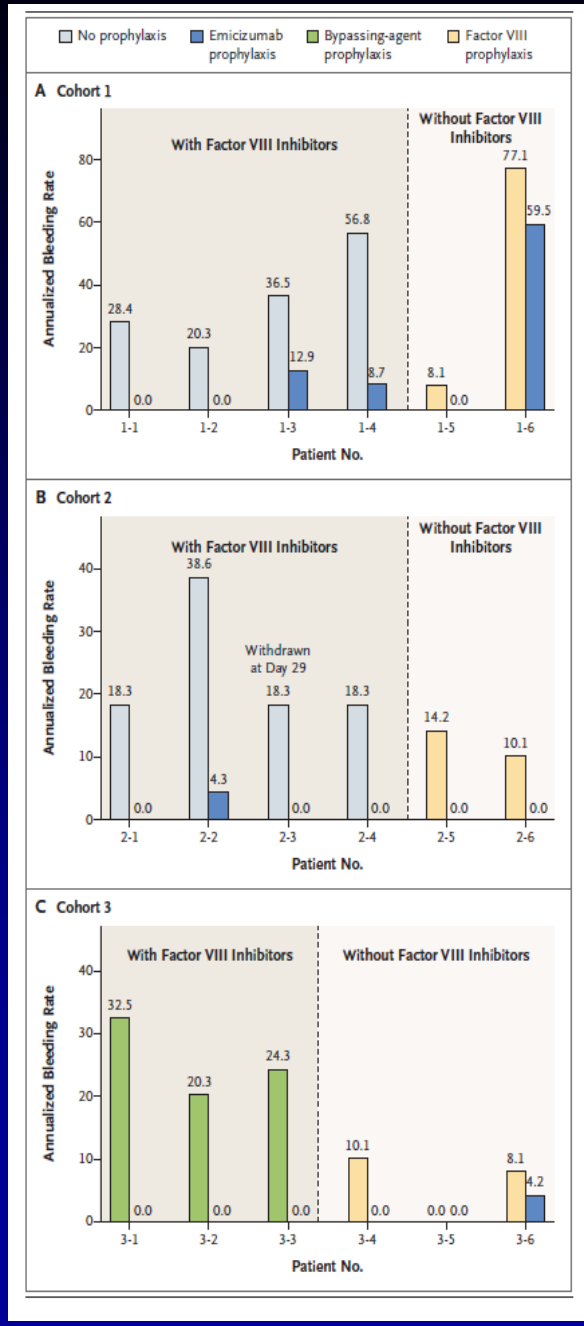
Factor VIII–Mimetic Function of Humanized Bispecific Antibody in Hemophilia A

Midori Shima, M.D., Ph.D., Hideji Hanabusa, M.D., Ph.D., Masashi Taki, M.D., Ph.D., Tadashi Matsushita, M.D., Ph.D., Tetsuji Sato, M.D., Katsuyuki Fukutake, M.D., Ph.D., Naoki Fukazawa, B.Sc., Koichiro Yoneyama, M.Sc., Hiroki Yoshida, M.Sc., and Keiji Nogami, M.D., Ph.D.

18 pazienti con emofilia A grave ricevevano settimanalmente emicizumab s.c. alla dose di 0.3, 1.0, o 3.0 mg/Kg (coorti 1, 2, 3, rispettivamente) per 12 settimane.

RESULTS

Emicizumab was associated with neither serious adverse events nor clinically relevant coagulation abnormalities. Plasma concentrations of emicizumab increased in a dose-dependent manner. Activated partial-thromboplastin times remained short throughout the study. The median annualized bleeding rates in cohorts 1, 2, and 3 decreased from 32.5 to 4.4, 18.3 to 0.0, and 15.2 to 0.0, respectively. There was no bleeding in 8 of 11 patients with factor VIII inhibitors (73%) and in 5 of 7 patients without factor VIII inhibitors (71%). Episodic use of clotting factors to control bleeding was reduced. Antibodies to emicizumab did not develop.



NEJM 2016; 374: 2044-53

Quali prospettive da disponibilità di prodotti non basati su terapia sostitutiva ?

Maggiore comodità d'uso (somministrazione s.c.; lunga durata d'azione).

Prevenzione e trattamento degli episodi emorragici in pazienti con e senza inibitori.

Prevenzione dell'inibitore.